VOLUME 63 NUMBER 1

ARCHIVES OF NEUROLOGY AND PSYCHIATRY

JANUARY 1950

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $12.00

Entered as Second Class Matter Jan. 7, 1919, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

Archives of Neurology and Psychiatry

VOLUME 63 JANUARY 1950 NUMBER 1

TUMORS OF THE BRAIN COMPLICATING PREGNANCY

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IN THE course of a neurosurgical practice, many problems aside from the brain tumor in question arise to plague the physician. Among them, none is more baffling than that presented when a pregnant woman is found to harbor a tumor in her brain. Both the life of the woman and that of the unborn child are at stake. Shall the pregnancy be interrupted? Shall the tumor be attacked without interfering with the course of the pregnancy? Shall the pregnancy be allowed to continue to its logical end and the tumor attacked later? What effect will labor have on a woman who already shows marked increase in intracranial pressure? It is probable that this pressure will be further increased during delivery. If the pregnancy is to be interrupted, should it be accomplished by induced labor or by cesarean section? Should a woman who harbors an inoperable and hopeless glioma of the brain have an abortion—with loss both of the fetus and, ultimately, of the patient—or should the former be saved if possible? Which is more important, a healthy baby or a woman who is doomed to die soon because of an inoperable glioma of the brain? Should the brain tumor be considered a complication of pregnancy or vice versa?

In a healthy woman pregnancy is not pathologic in itself and in the great majority of cases it runs a normal and innocuous course. This may not be true in the case of a pregnant woman with a tumor in her brain. The problem is further complicated by the many varieties of neoplasms, which may occupy almost any location in the brain. Some of them, such as meningiomas, are usually benign and of slow growth. But even the meningioma may be so located as to present fulminating symptoms. The early stage of an acoustic neurinoma presents few symptoms; in its later stages this relatively benign growth may cause both disabling and alarming symptoms, owing to increased intracranial pressure.

The problem becomes more acute and complex when any of the glioma group is present. Their course is unpredictable. They vary

Read at a meeting of the Southern California Neurosurgical Society, April 30, 1948.

greatly in rapidity of growth and may occur in any part of the brain. It is usually a safe axiom that an astrocytoma or a glioblastoma should be attacked as soon as the diagnosis is made. Such a tumor cannot safely wait, as will be seen, especially in a pregnant woman.

It is strange that more emphasis has not been placed on brain tumor as a complicating factor in pregnancy. Cushing [1] referred to a case encountered in a young housewife in which the precipitation of symptoms of increased intracranial pressure during the course of a pregnancy obscured the diagnosis. Increasingly severe suboccipital headaches and vomiting, which at the time were ascribed to toxemia, resulted in the pregnancy being interrupted at the eighth month, "a healthy child surviving." Her headaches and vomiting, however, continued after the delivery and were soon accompanied with rapidly failing vision. It was not until three months later that a tumor of the brain was suspected. During the ensuing three years a midcerebellar cystic hemangioma was attacked at four sittings, with a fatal outcome from pneumonia after the fourth operation. The case is interesting not only from the standpoint of the confusion of the picture by the pregnancy early in the disease but also because it was among the first in which the electrosurgical unit was employed as a desiccating agent. In his comment, in summing up the case, Cushing stated:

> The coincidental pregnancy, to which the patient's excessive headaches and vomiting were ascribed, served so to obscure the early diagnosis in this case that she was nearly blind before tumor was suspected. Pregnancy, however, appears to be a not uncommon provocative element in bringing tumors to light, more particularly perhaps angiomatous lesions.

The same statement would hold equally true for any other type of brain tumor.

REPORT OF CASES

CASE 1.—*Death of a 33 year old woman in her fifth month of pregnancy, from an astrocytoma of the pons.*

P. F., a 33 year old white woman, was admitted to the Los Angeles County Hospital on May 16, 1944. For a year previously she had noticed ringing in both ears, more pronounced in the left. Severe headaches in the left occipital region, associated with periods of diplopia and dimness of vision, developed. For the eight weeks prior to her admission progressive weakness of the left arm and leg had been present. She also experienced difficulty in speaking and inability to say the words she was thinking. Numbness of the right side of the face appeared.

Examination revealed an alert, obese, quiet woman who was in no acute distress. Her temperature was 98.6 F., her respiration rate was 20 and her pulse rate 86, per minute. The blood pressure registered 132 systolic and 76 diastolic. There was rapid horizontal nystagmus with the quick component to the left. The eyegrounds were normal. The corneal reflex was absent on the right. There

1. Cushing, H., and Bailey, P.: Tumors Arising from the Blood-Vessels of the Brain, Springfield, Ill., Charles C Thomas, Publisher, 1928, pp. 167-178

was mild weakness of the left side of the face of central type. The right ear was moderately deaf, with lateralization to the right side in the tuning fork test. Pronounced hemiparesis on the left side with astereognosis on the same side was evident. The deep reflexes on the left were hyperactive as compared with those on the right. The Babinski, Oppenheim and Gordon signs were strongly positive on the left and weakly so on the right.

The uterus was of a size consistent with a five month pregnancy, and fetal heart tones were audible.

Laboratory Findings.—The spinal fluid was crystal clear. It was under 140 mm. of pressure, contained 4 lymphocytes per cubic millimeter and gave a negative reaction to the Pandy test for globulin. Smears and cultures of the spinal fluid revealed no pathogens, and the reaction to the Wassermann test was negative.

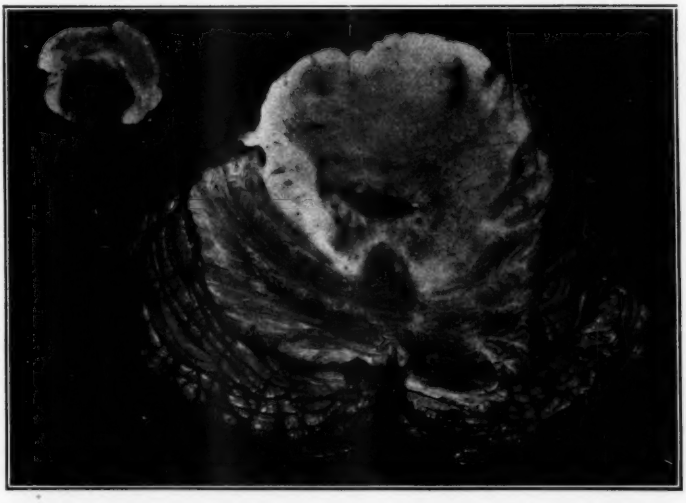

Fig. 1 (case 1).—Gross appearance of the infiltrating astrocytoma of the pons and medulla.

The hemoglobin was 68 per cent; the white blood cell count was 9,250, with 62 per cent polymorphonuclear leukocytes. The Wassermann reaction of the blood was negative. The urine was entirely normal.

Course.—The symptoms present on admission became progressively worse. Pulmonary edema developed, with the temperature rising to 104 F., and she died at 5:30 p. m., on May 31.

Autopsy.—The uterus was enlarged to the level of the umbilicus and contained a 5 month old fetus, which measured 28 cm. in length. Examination of the brain revealed an infiltrating tumor occupying the right cerebellopontile angle and evidently arising from the pons (fig. 1). The pons itself was diffusely enlarged, the enlargement being greater on the right side. The tumor was rather smooth, but somewhat lobulated. The trigeminal nerve on the right was considerably flattened and distorted. On section the margins of the tumor were indistinct, but it could be ascertained that the growth extended into the medulla.

Microscopic examination (fig. 2) revealed a uniformly cellular tissue, with an abundance of connective tissue.

Diagnosis.—The diagnosis was astrocytoma of the pons.

Comment.—Gliomas of the pons are invariably invasive and seldom give rise to signs of increased intracranial pressure. Such was the case in this woman. The fifth, seventh and eighth cranial nerves on the right were chiefly affected. The pyramidal tracts, as well as the ascending sensory pathways, on the right were also involved, giving rise

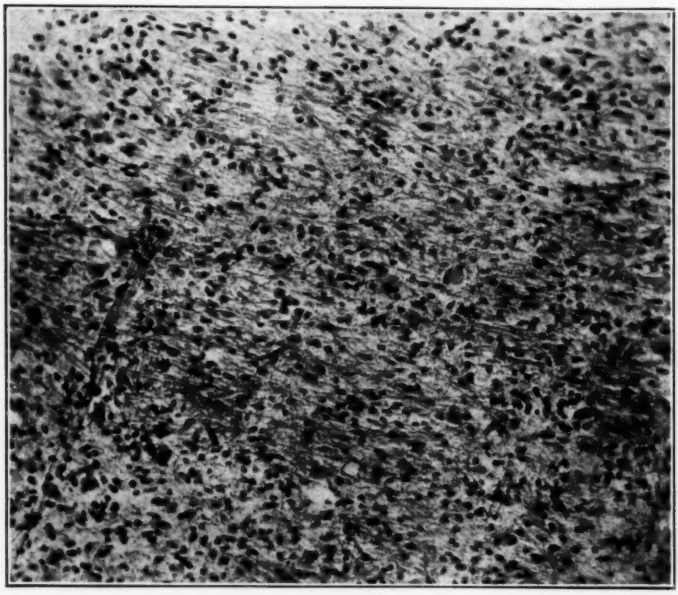

Fig. 2 (case 1).—Microscopic character of the tumor, a typical astrocytoma.

to the left hemiparesis and astereognosis. In the circumstances, a fatal outcome to both mother and child was inevitable.

CASE 2.—*Death of a 41 year old housewife, in the seventh month of pregnancy, from astrocytoma of the left frontal lobe.*

M. H., aged 41, a French-Canadian Indian, a housewife, was admitted to the Los Angeles County Hospital on March 18, 1941, in her seventh month of pregnancy. She had already borne ten children. For the preceding six weeks she had shown unsteadiness of gait and hoarseness. Urinary incontinence had been present for two weeks; nausea and vomiting, for one day. No mention was made of headache. Her gait was unsteady, but there was no evident motor paralysis. Tumor of the brain was not suspected.

Examination revealed an obese Indian woman, who was very drowsy and difficult to arouse. She could not speak above a whisper. She was cyanotic, with

frothy fluid coming from her mouth. The pupils were equal and reacted to light. The optic disks were flat and showed normal cupping. The heart was regular, and the heart sounds were clear. Examination revealed many rhonchi throughout the lungs.

The uterus was enlarged to the size consistent with that of a seven to eight month pregnancy. Fetal heart sounds were not heard. There was no peripheral edema. The deep reflexes were hyperactive bilaterally, and the Babinski sign was elicited on both sides.

The temperature was 98 F.; the pulse rate 96, and the respiration rate, 22. The blood pressure was 130 systolic and 64 diastolic. The Wassermann and Kahn reactions of the blood were negative. The hemoglobin measured 11.5 Gm.; the

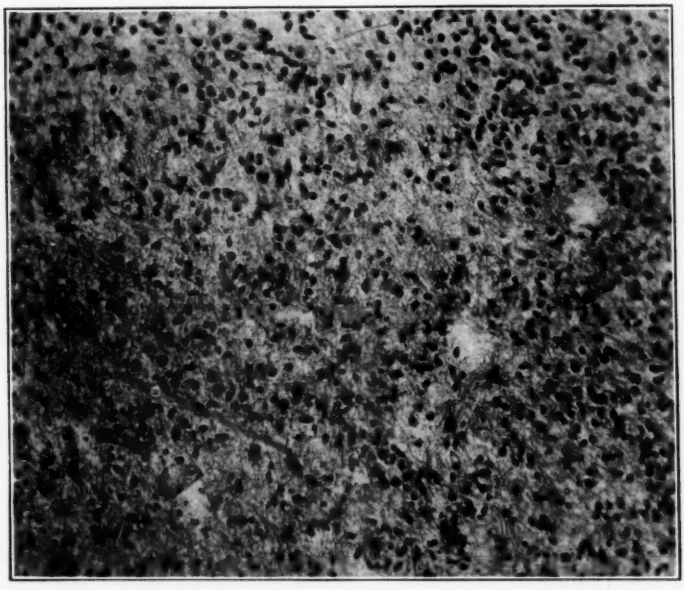

Fig. 3 (case 2).—Microscopic appearance of an astrocytoma of the left frontal lobe, showing malignant tendencies.

white blood cell count was 19,000, with 80 per cent polymorphonuclear leukocytes; urinalysis was noncontributory.

Nine hours after admission the patient became deeply cyanotic and comatose. Her temperature rose to 105 F. The spinal fluid was clear and colorless, and contained 3 lymphocytes per cubic millimeter; the pressure was 400 + mm.; the reaction to the Pandy test was negative. She died twenty hours after admission.

Autopsy.—The uterus was enlarged and reached 3 fingerbreadths below the xiphoid process. The wall of the uterus measured 12 mm. in its thickest portion. A 45 cm. fetus within the uterus appeared to be in good condition.

Examination of the brain showed swelling of the left gyrus rectus consistent with invasion of the cortex. Coronal sections revealed a tumor deep in the left frontal lobe, the mass bulging into the left lateral ventricle. The tumor extended back

and partially replaced the head of the caudate nucleus. The posterior portion of the tumor showed hemorrhage into its substance. The tumor measured 5.2 by 4.2 by 3.9 cm. in various diameters. The gross diagnosis was glioma of the left subfrontal region, involving the anterior extremity of the corpus callosum.

Diagnosis.—The basic growth was an astrocytoma (fig. 3). Signs of increased malignancy were evident in more active cellular proliferation and the areas of necrosis.

The clinical diagnosis was astrocytoma with malignant tendencies.

Comment.—This tumor was unsuspected during the patient's life. The woman was between her seventh and eighth month of pregnancy, but the fetal heart sounds could not be heard. Apparently, the fetus was dead at the time of the mother's admission to the hospital, since she herself was moribund at this time.

CASE 3.—*Sudden death of an expectant mother in her seventh month of pregnancy, from hemorrhage into a cystic astrocytoma of the left cerebellar hemisphere.*

S. B., aged 17, a white woman, was admitted to the Los Angeles County Hospital on Aug. 31, 1947, in the seventh month of her pregnancy. Six weeks after her last menstrual period, on Jan. 28, 1946, she experienced a severe constant throbbing occipital headache. This headache continued almost without let-up. Nausea and vomiting soon set in and continued throughout the course of her illness. The vomiting occurred chiefly in the morning and was thought to be "morning sickness," frequently present in the early months of pregnancy. She vomited three or four times a day. About two months before her admission blurring vision appeared, which was followed by diplopia. During the month before her admission to the hospital, she lost 12 pounds (5.4 Kg.) in weight. Difficulty in walking was attributed to weakness.

Examination.—The patient was seven and a half months pregnant, and obviously very ill. She was somewhat pale and complained bitterly of occipital headache. Suboccipital tenderness was present. There was paralysis of the left abducens nerve. Horizontal nystagmus was present on her looking both to the right and to the left, but was greater on her looking toward the right. Slight vertical nystagmus was noted on upward gaze. There was 2 D. of choking of both disks, with several fresh hemorrhages scattered throughout the retinas. The neck was rather resistant to flexion. The left arm was noticeably ataxic with adiadokokinesis and dysmetria. Otherwise, the neurologic examination revealed nothing remarkable.

An electroencephalogram on September 4 showed a moderate amount of diffuse abnormal activity, with phase reversal in the left occipital region. A roentgenogram of the skull revealed an unusual degree of convolutional markings but was otherwise noncontributory.

The abdominal findings were consistent with a seven and one-half month pregnancy, the fundus of the uterus reaching 21 cm. above the symphysis. Fetal heart sounds were of good quality, with a rate of 140 per minute. A roentgenogram of the abdomen showed one fetus of about 7 months, in the left occipital transverse position.

Laboratory Data.—The urine was normal. The spinal fluid was crystal clear; the pressure was 200 mm.; the cell count was 6 per cubic millimeter, and the Pandy reaction was negative. The Wassermann reaction of the blood was negative. The

nonprotein nitrogen was 29 mg. per hundred cubic centimeters. The blood pressure was 120 systolic and 86 diastolic.

Course.—It was felt that the patient had a tumor of the left cerebellar hemisphere, and a prompt suboccipital exploration was planned. She died very suddenly on September 10, the day before that on which her craniotomy was scheduled.

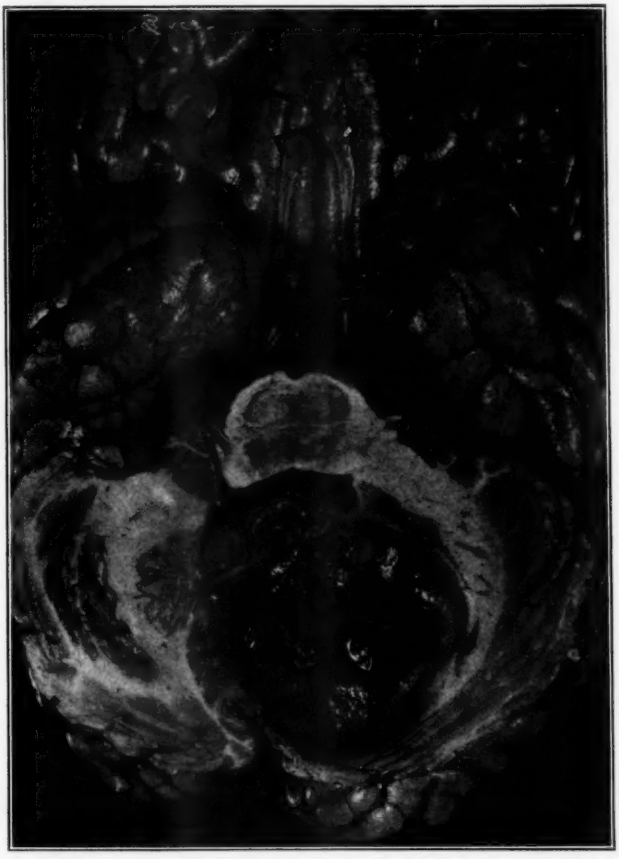

Fig. 4 (case 3).—Horizontal section through the pons and cerebellum, showing a large cystic astrocytoma. The fresh hemorrhage into the tumor proved suddenly fatal.

Autopsy.—The uterus filled the pelvis and two thirds of the abdominal cavity. It contained a 6½ month male fetus.

The convolutions of the brain were generally flattened, and there was herniation of the cerebellar tonsils into the foramen magnum. Horizontal section of the pons and cerebellum revealed a large, grayish yellow tumor, which was sharply

delimited from the surrounding cerebellum (fig. 4). It contained in its center a cyst of irregular shape, measuring 2.3 by 1.6 cm. in its greatest diameters. A hemorrhage containing freshly clotted blood was found in the posterior and medial margins of the tumor. The tumor itself measured 4.3 by 3.8 cm. in its greatest diameter. The unchanged portion of the tumor was of uniform texture and presented a finely granular appearance.

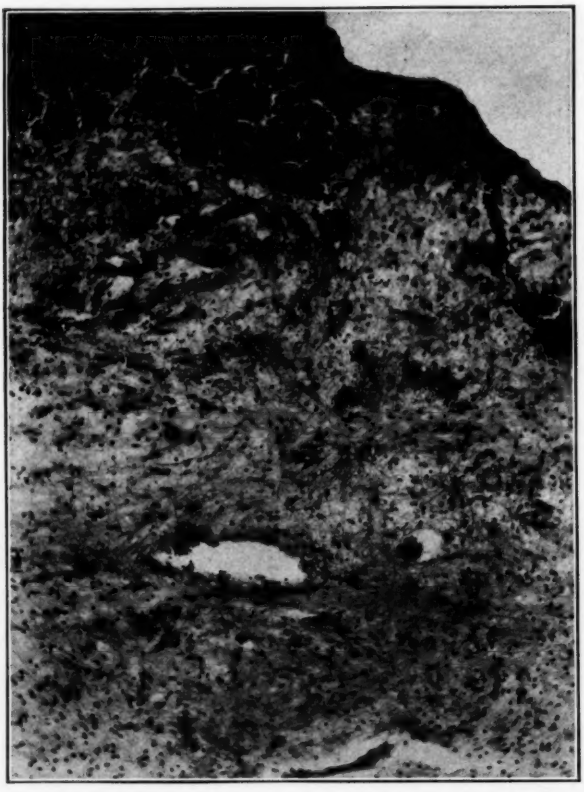

Fig. 5 (case 3).—Microscopic appearance of the astrocytoma, showing softened area invaded by hemorrhage.

Histopathologic Examination.—Microscopically, the tumor consisted of a finely reticular stroma, in which there was a profusion of small, round and oval nuclei, which showed moderately dark staining (fig. 5). The blood vessels showed moderate endothelial proliferation with perivascular condensation of neuroglia and slight monocytic infiltration. In one area of the tumor there was evidence of recent hemorrhage in a necrotic area. There was no evidence of mitotic figures or of cell division.

Diagnosis.—The diagnosis was cerebellar astrocytoma.

Comment.—The treachery of cystic cerebellar astrocytomas is well known. This patient died suddenly, during observation on ward rounds, of a hemorrhage into the substance of her tumor. Such an event could not be anticipated. In retrospect, it seems likely that she would have been temporarily benefited by suboccipital decompression, which had been planned for the following morning. A rapid postmortem cesarean section should have been considered, as it might have resulted in a living child. In several recorded cases, prompt postmortem section has resulted in saving the baby.

CASE 4.—*A 20 year old Negro woman with right acoustic neurofibroma, who was carried safely through pregnancy. Tumor removed later.*

E. H., a 20 year old Negro woman, was admitted to the Los Angeles County Hospital on Sept. 26, 1939. She was delivered of a normal living male infant with low forceps on September 27. Her period of gestation was accompanied with constant nausea, vomiting, headache and edema.

For a year previously she had had ringing in the right ear with rapidly increasing deafness. The left ear was not affected. Blurring vision, with difficulty in reading, had been present about a year. For ten months her gait had become increasingly unsteady, and shakiness of the right hand and arm developed. At about the onset of her pregnancy, headache appeared in the left frontal area. This headache continued and was associated with dizziness and vomiting. The vomiting was attributed to her pregnancy. At times she noticed shooting pain in the right side of her face.

Examination.—The general physical condition was good. There was severe suboccipital tenderness. The eyegrounds showed edema of the nasal margins of the disks, with a suggestion of swelling, but were otherwise unremarkable. Horizontal nystagmus was present in looking in either direction, but was greater on looking to the right. There was weakness of the right abducens nerve with diplopia when looking toward the right. The right side of the face was flattened and showed high grade weakness of the peripheral type. Hearing was severely impaired in the right ear. Caloric tests revealed normal response of all canals on the left, and no response of the horizontal canal and only slight response of the vertical canals on the right.

There was mild hemihypalgesia on the right, but no definite motor weakness was anywhere present. The right arm and leg showed definite hypotonia with ataxia, dysdiadokokinesia and rebound phenomena. The Romberg sign was elicited, and she tended to reel to the right when walking. The biceps and triceps jerks were quicker on the right than on the left, but the knee and ankle jerks could barely be obtained. There were no abnormal reflexes of the Babinski group; the ankles were not edematous.

The spinal fluid was clear and colorless and was under 400 mm. of pressure. The cell count was 7 lymphocytes per cubic millimeter, and the total protein content, 0.13 Gm. per hundred cubic centimeters. The Wassermann reaction of the blood was negative.

Roentgenograms of the skull in Towne's position showed erosion of the right petrous ridge in the region of the internal auditory meatus, which was enlarged.

Operation.—On October 19, a right acoustic neurofibroma was encountered at operation. An intracapsular removal of about three quarters of the growth was accomplished.

Microscopic examination revealed a fibrous type of tumor with some reticular tissue (fig. 6). The atypical pseudo palisading was characteristic. The reticular portions were extensive, with fairly large, round nuclei.

Postoperative Course.—The postoperative course was uneventful except for complete paralysis of the right side of the face, incident to injury of the facial nerve when the tumor was attacked. She was discharged on November 24.

Comment.—The acoustic neurofibroma was not suspected in this case until after the patient had been delivered. The continuance of headache, dizziness, nausea and vomiting after delivery indicated that these

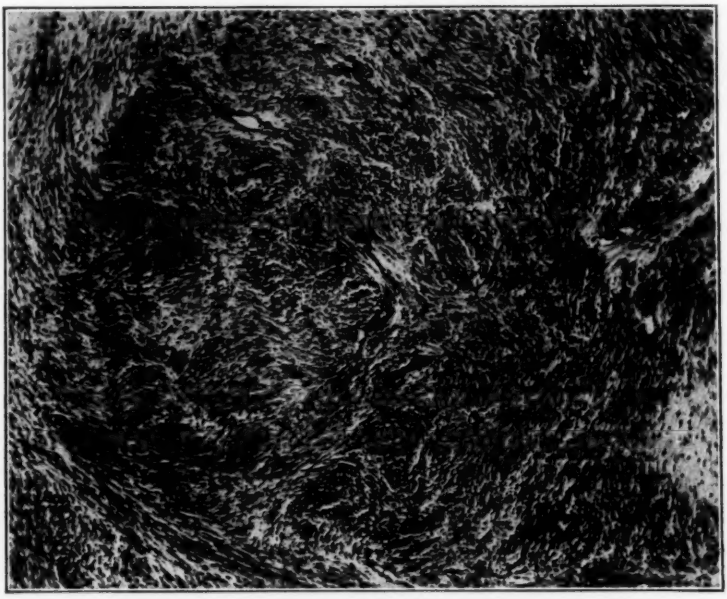

Fig. 6 (case 4).—Microscopic appearance of the acoustic neurofibroma, showing characteristic palisading of elongated nuclei and whorls of these tumors.

symptoms were not due to toxemia of pregnancy. The neurologic diagnosis was clearcut. Full-blown cerebellar signs had not developed at the time the baby was born; this probably accounted for the fact that the delivery was not hazardous.

CASE 5.—*Two normal pregnancies in the presence of a meningioma of the sphenoidal ridge; subsequent successful removal of the tumor.*

G. S., a Negro woman aged 27, a housewife, first became a patient at the eye clinic of the Los Angeles County Hospital on July 31, 1947, because of blindness and bulging of the left eye. Five years previously she had first noticed blurring of vision in the left eye. Soon after this she became pregnant and was

delivered normally of a baby boy at the White Memorial Hospital on Nov. 9, 1943. During her pregnancy, her physician told her that the left eye bulged. During the last four months of this pregnancy she experienced a constant dull aching pain in the left parietal region; this pain disappeared after delivery. The left eyelid drooped noticeably during the pregnancy, but the ptosis, too, lessened after the baby was born.

Slowly the exophthalmos and failing vision in the left eye progressed, up to the beginning of her second pregnancy, about March 1947. She was admitted to the neurologic service on September 30, because of headache, blindness in the left eye, frequent tingling sensations about the left eye, increased lacrimation and numbness of the left side of her nose and upper lip.

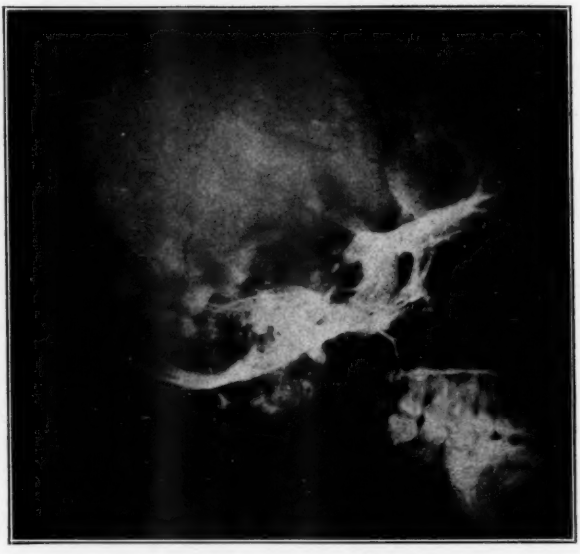

Fig. 7 (case 5).—Roentgenogram of the skull, showing increased density of the greater and lesser wings of the left sphenoid bone, due to thickening of these structures.

At this time she was about six months pregnant. The left eye was noticeably protuberant, and she had tenderness over the left temporal region. She was totally blind in the left eye, and examination of the fundus showed complete primary optic nerve atrophy. The pupil was fixed to direct light but reacted consensually. The right fundus showed some blurring of the disk and overfilled vessels.

Her spinal fluid was clear and colorless and under 300 mm. of pressure, with normal dynamics; the Pandy test gave a negative reaction for globulin; the total protein measured 0.04 Gm., the chlorides 676 mg. and the sugar 88 mg., per hundred cubic centimeters, and the Wassermann reaction was negative. The Wassermann reaction of the blood was negative. The blood pressure was 100 systolic and 60 diastolic. The urine was normal, with a specific gravity of 1.018.

Roentgenograms of the skull showed increased density of the greater and lesser wings of the left sphenoid bone, as well as an actual increase in the bony substance, which projected into the floor of the middle fossa (fig. 7). In short, the picture was one of pterional meningioma.

A diagnosis of meningioma of the sphenoidal ridge of the left side was made. As her neurologic status in general was normal and her pregnancy was progressing favorably, she was discharged on Oct. 14, 1947, to be followed in the outpatient department. She was readmitted to the obstetric service on Dec. 26, 1947 and had an uneventful spontaneous delivery of an 8 pound 8 ounce (3,856 Gm.) male infant at 8:29 p. m. She left the hospital with her baby on December 31.

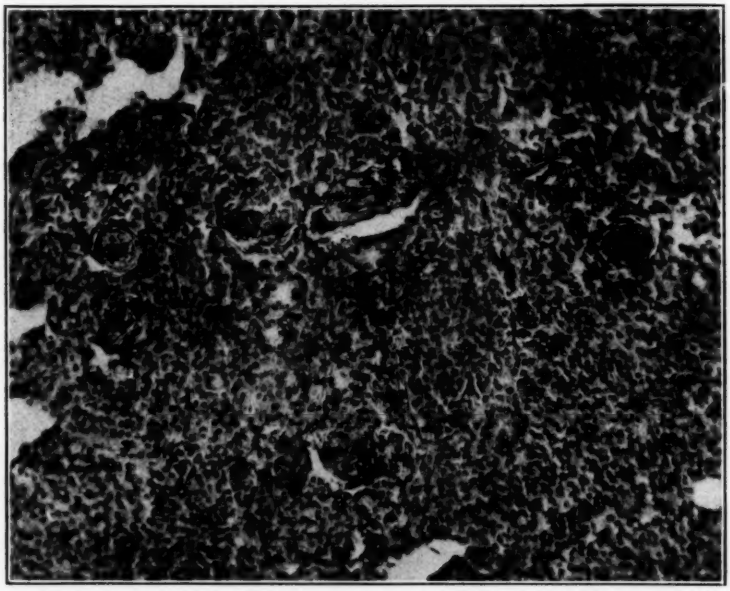

Fig. 8 (case 5).—Microscopic section of a syncytial type of meningioma with discrete areas of calcification attesting to its chronicity.

She was again admitted to the neurosurgical service on Feb. 23, 1948. In the interim a burning sensation had developed over the left side of her face. The nonpulsating exophthalmos on the left side was a little more marked, but, except for the development of hypesthesia over the sensory distribution of the first and second divisions of the left trigeminal nerve, her condition was the same as previously recorded. The spinal fluid at this time showed a pressure of 325 mm., no cells and a total protein of 0.18 Gm. per hundred cubic centimeters.

An electroencephalogram on Feb. 25, 1948 showed occasional 6 to 7 per second waves from the left anterior temporal-frontal area.

On March 6, a meningioma of global type was removed piecemeal from the left sphenoidal ridge and floor of the middle fossa. The left optic nerve was not visualized. She made an uneventful recovery.

Microscopic examination (fig. 8) showed a fairly cellular tumor of uniformly shaped cells and nuclei, lying in a homogeneous syncytium. Deposits of calcium were seen in the walls of the blood vessels, attesting to the chronicity of the tumor.

Diagnosis.—The diagnosis was syncytial meningioma with calcium in the blood vessels.

Comment.—It has been said that pregnancy hastens the growth of a brain tumor. We have no concrete evidence that this is true, although it is our impression that the altered metabolism of the body at this time may accelerate tumor growth. This patient's symptoms of headache and paresthesia over the left side of her face were increased during the periods of her two pregnancies. At no time did she show signs of toxemia of pregnancy.

CASE 6.—*Cyst of the right cerebellar hemisphere in 1936; incomplete removal of the cyst (astrocytoma?). Delivery of a 7 pound 10 ounce (3,459 Gm.) female living baby by forceps in 1941. Signs of recurrence of her cerebellar tumor in 1948.*

B. L., aged 25, was admitted to the Los Angeles County Hospital on Oct. 30, 1936, with the complaint of occipital headaches, failing vision and ataxia. Six months previously she first had difficulty in walking, with occasional staggering toward the right. About this time headaches, which had previously been orbital, shifted to the right occipital region and became severer. At times her whole head hurt. She also encountered difficulty in controlling the movements of her right hand and arm. Her eyesight began to fail, reaching the point at which she could no longer read.

The general physical examination was essentially noncontributory. There was extreme tenderness in the right occipital region, and her neck was resistant to flexion. The eyegrounds revealed extreme bilateral choking of the disks, with embedding of the vessels, a few scattered hemorrhages and papilledema of 5 to 6 D. The pupils reacted poorly to light. There was barely perceptible weakness of the right side of the face, of central type. Her speech was greatly slurred and of nasal quality. She showed pronounced hypotonia, ataxia and adiadokokenesia of the right upper extremity. The Romberg sign was positive, with a tendency to fall toward the right. Her gait was unsteady, with deviation toward the right. A diagnosis of tumor of the right cerebellar hemisphere was made.

Roentgenograms of the skull revealed nothing abnormal. The Wassermann reaction of the blood was negative.

On Nov. 9, 1936 a large gliomatous cyst was uncovered in the right cerebellar hemisphere. It was encountered at a depth of 3 cm., and 25 cc. of heavy, syrupy yellow fluid was removed by tapping. Because of her poor condition the wound was closed without further treatment.

On November 16, the wound was reopened and a subcortical cyst, which almost filled the right cerebellar lobe, was uncovered. What was believed to be a mural nodule was removed, but microscopic examination of the tissue revealed no tumor cells. Grossly, the tumor resembled a cystic astrocytoma.

After this surgical procedure, the patient's general condition greatly improved; the papilledema subsided; headaches and vomiting stopped, but she was still slightly unsteady on her feet.

She was readmitted to the obstetric service of the hospital on March 6, 1941, with moderately severe hyperemesis gravidarum and acidosis, which had developed since the onset of her pregnancy, two months previously. She was lethargic, toxic and dehydrated. The uterus was the size consistent with a two month pregnancy.

Her condition quickly cleared up under treatment, and she did not return to the clinic. On Sept. 19, 1941 she was delivered at another hospital of a 7 pound 10 ounce female child without difficulty.

When she was seen again, on Jan. 22, 1948, she indicated that during the past year there had been a recurrence of headache, dizziness and a tendency to fall backward. Her cerebellar wound was well healed and showed no bulging or signs of pressure. She had advanced secondary optic nerve atrophy. Her coordination was good, and she showed few, if any, signs of cerebellar derangement.

Comment.—While the diagnosis in this case has not been verified microscopically, there is no doubt that the patient had a cystic tumor of the right cerebellar hemisphere in 1936. Her pregnancy followed five years later, at which time she had few signs of increased intracranial pressure. It is probable that she still has a tumor of the cerebellum, which we suspect to be an astrocytoma. Recent recurrence of symptoms may lead to another exploration.

CASE 7.—*Normal pregnancy and delivery fourteen months after evacuation of a gliomatous cyst in the left occipital lobe. Cystic astrocytoma removed later.*

J. D., aged 19, was referred by Dr. Clarence H. Nelson on Oct. 24, 1946, because of failing vision and headaches. These symptoms had appeared ten months previously, in December 1945. The pain was always in the back of her head, being sometimes greater on the right and at others on the left. It became very severe and almost constant, and was accompanied with nausea and vomiting.

Because of failing vision, she was fitted with glasses in January 1946, without relief. She noticed that she did not see objects to the right as well as to the left and decided that her "right eye couldn't see as well as the left." She experienced occasional "blind spells," which lasted about two minutes. At times her right hand "would feel as if it was going to sleep." Occasionally she had noted disturbance in speech, when she "could think of the right word but could not say it."

Examination showed that she was in good general physical condition. There was long-standing choking of both disks, with complete obliteration of the margins, embedding of both arteries and veins, piling up of new tissue in the optic cups and 6 D. of papilledema. A complete right lower homonymous quadrantanopsia existed (fig. 9 *A*). There was slight sensory loss in the right hand. The deep reflexes were all lively and equal on the two sides. The Babinski sign was elicited on the right and was absent on the left. Ankle clonus was present on the right in a few tests, but was not elicited on the left. A roentgenogram of the skull showed thinning of the posterior clinoid processes and increased convolutional markings. An electroencephalogram showed abnormal electrical activity in the left occipital area. The Wassermann reaction of the blood was negative.

At operation, on Nov. 1, 1946, a large subcortical cyst was drained from the left parieto-occipital region. The fluid was syrupy and canary yellow. More than 200 cc. of fluid was removed. It was believed that this cyst represented a deep-seated cystic astrocytoma, but as no tumor presented on the surface of the brain, the cortex was not disturbed.

The patient showed marked improvement and gained weight, and the visual fields returned to normal (fig. 9 *B*). She then married and became pregnant about April 1947. She was watched carefully during her pregnancy, but at no time did she show any signs of recurrence of her former symptoms. She was delivered by instruments on Jan. 17, 1948 of a healthy baby girl.

Because of a recurrence of symptoms, a second operation was performed on May 26, 1948, when the presence of a cystic astrocytoma of the left parieto-occipital lobe was verified and the tumor incompletely removed. She stood the procedure well.

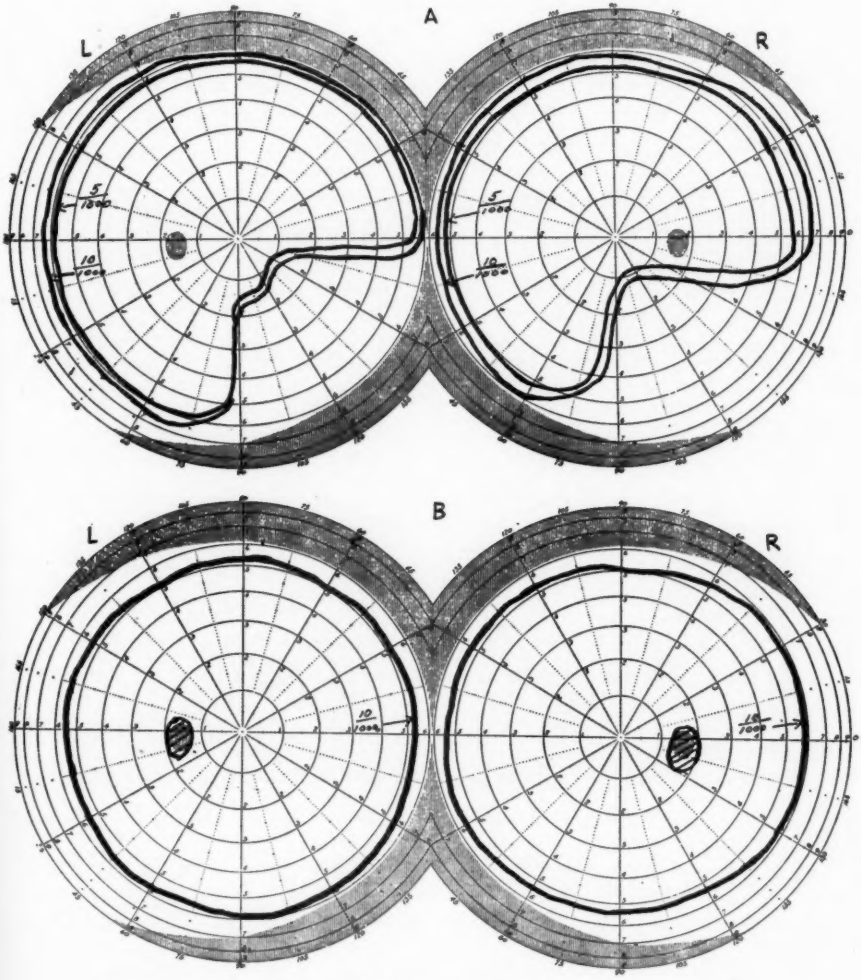

Fig. 9 (case 7).—*A*, visual fields (Oct. 24, 1946), showing lower right homonymous quadrantanopsia due to a cystic tumor in the left occipital lobe. Visual acuity, without correction, was 20/20 in each eye.

B, recovery of visual fields on Jan. 5, 1948, fifteen months after emptying of the cyst. Visual acuity, without correction, was 20/20-2 in the left eye and 20/20-1 in the right eye.

Microscopic examination revealed a typical astrocytoma (fig. 10).

Comment.—During her entire period of pregnancy, this woman had a cystic astrocytoma of the left cerebral hemisphere. Earlier emptying of the cyst had relieved all pressure symptoms, permitting an uneventful period of pregnancy and a normal delivery. Four months after delivery, recurrence of symptoms demanded further exploration, with incomplete removal of the tumor. Recurrence is again anticipated and sterilization advised. Another pregnancy would reopen the whole question of procedure, with a more serious outlook than before.

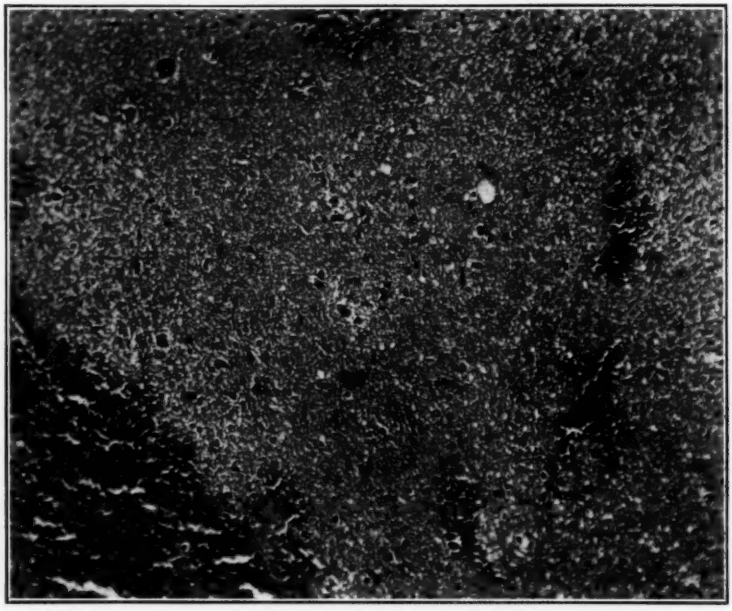

Fig. 10 (case 7).—Microscopic appearance of the astrocytoma.

CASE 8.—*A woman harboring a tumor of the pituitary gland with appearance of visual symptoms during pregnancy; normal delivery at term. Observation for fourteen years. Several courses of high voltage roentgen therapy, with beneficial results.*

On May 2, 1934, Drs. M. Beigelman and M. J. Abramson, of Los Angeles, referred S. A., a married housewife, aged 32, because of failing vision. She had been delivered of her second child two weeks previously. Her menses had become irregular and scanty for several months prior to her last conception. There was one older child, a girl of 6 years. The birth of her last baby had presented no difficulties from an obstetric standpoint.

At about the seventh month of her last pregnancy, she "noticed trouble" with her eyes. Her vision began to blur, and she had difficulty in reading. She noticed

that "things seemed shut off from the side" and that her eyes did not focus properly. Headaches had been occasional, but were not severe and were easily controlled by taking 2 tablets of anacin®.[2] There was no nausea or vomiting.

Examination, two weeks after delivery, showed moderate enlargement of her thyroid gland. She stated that such an enlargement had occurred during both her pregnancies; otherwise the general physical examination showed nothing abnormal.

The optic disks were sharply outlined and appeared a little paler than normal. The veins were full and pulsated, and the arteries were of good caliber. Neither fundus gave the the impression of primary optic nerve atrophy.

The visual fields on May 2, 1934 showed an incomplete, but marked, tendency toward bitemporal hemianopsia (fig. 11). Roentgenograms of the skull (fig. 12) revealed enlargement of the sella turcica with pronounced thinning of the posterior clinoid processes. The floor of the sella was thinned and was pushed downward

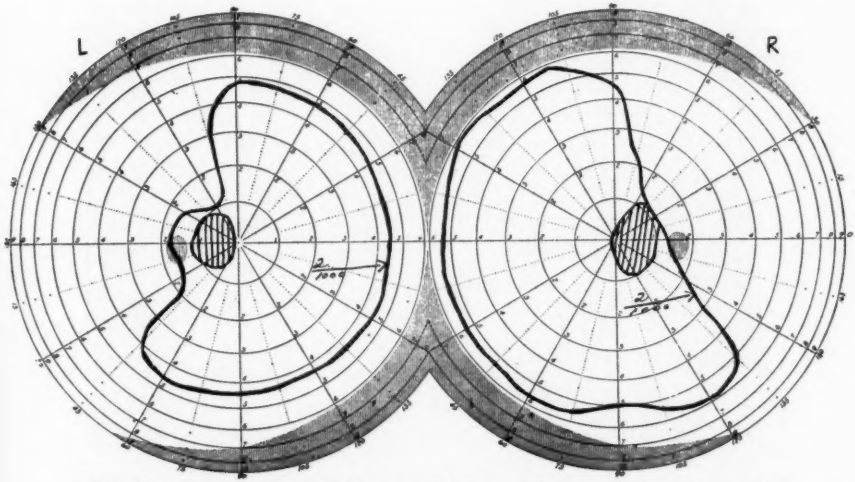

Fig. 11 (case 8).—Visual fields in a patient with tumor of the pituitary gland taken two weeks after delivery. Visual acuity, uncorrected, was 20/30 in the left eye and 20/40 in the right eye. An incomplete bitemporal hemianopsia was present at this time and has remained unchanged.

into the sphenoid sinus. The finding represented an irregular type of enlarged sella turcica.

Except for the ocular changes and the enlarged sella turcica, her neurologic status was normal at that time (May 2, 1934) and has remained so since, a period of fourteen years. She was considered to have a pituitary tumor, probably a chromophobe adenoma, which had undergone physiologic enlargement during her pregnancy. Because of further contraction of the temporal fields and further enlargement of the blindspots during the ensuing six months, it was decided to give her high voltage roentgen therapy. This was carried out by Dr. R. G. Taylor. Her therapy record follows: "In 1935, between the dates of January 3 and January 15, the patient had 1,000 r, measured in air, to each temple, the radiation

2. Anacin® contains 3 grains (0.19 Gm.) of acetophenetidin per tablet with unnamed amounts of acetylsalicylic acid, caffeine and quinine sulfate.

factors being 200 kilovolts peak, 0.75 mm. copper filter, 50 cm. distance and a 5 by 5 cm. field. The next series of radiation therapy was given between March 29 and April 12, 1937, when she had 1,484 r to the right temporal field and 1,486 r, measured in air, to the left temporal field. She had another course of therapy over the period from Nov. 1 to Nov. 18, 1943, amounting to 1,504 r to the left temporal field and 1,467 r to the right. She was last seen by us on Jan. 6, 1944, when she had depilation over the treated area with no telangiectasis or other changes in the skin."

The fields improved after these treatments. After six months contraction of the temporal fields again increased and then remained stationary until about March 1937, when further contraction occurred. Her second course of high voltage roentgen radiation was given from March 20 to April 12, 1937, which resulted

Fig. 12 (case 8).—Roentgenograms showing enlargement and ballooning of the sella turcica in a patient with tumor of the pituitary gland.

in another improvement in her visual fields, an improvement which lasted for approximately five years. Her third, and last, course of roentgen treatments was given from Nov. 1, 1943 to Nov. 18, 1943, resulting in a superficial burn of each malar region. Because of this reaction it was decided that further irradiation was contraindicated.

As a result of these three courses of roentgen treatment, covering a period of fourteen years, her vision has remained essentially unchanged. The eyegrounds have shown slowly increasing pallor of the optic disks, although they have never approached the stage of advanced primary optic nerve atrophy, and the caliber of the vessels has remained good. The visual acuity has stood up well.

	Left Eye	Right Eye
1934	20/30	20/40
1948	20/20	20/20

The sella turcica has shown but little change, remaining a ballooned type with moderate enlargement.

The menstrual history has shown alterations in the frequency and amount of flow. When she was first seen, at the age of 32, she had been delivered two weeks previously. Her menses had been scanty and irregular for about five months before conception. Menstruation was reestablished on Oct. 25, 1935, approximately eighteen months after delivery, but was scanty and irregular for the ensuing year. By Nov. 9, 1936 her periods were full and regular and remained so until May 1945. She was then 44 years old and approaching the menopause. Now, at the age of 46, menstruation has practically ceased.

Comment.—During the fourteen year period of observation, she has had occasional headaches, which at times have been accentuated by attacks of frontal sinusitis. On occasion she has complained of transient sharp, shooting pains in the temples. Slight increase in the size of the sella turcica with advance in the erosion of the posterior clinoid processes has taken place. Her vision has at all times shown an incomplete bitemporal hemianoptic contraction, but her acuity has remained good and there has been little advance in the sharpness or pallor of the optic disks. Her limit of radiation has been reached, and exploration of the pituitary region is anticipated when, and if, the optic nerves appear to be further jeopardized by pressure. What influence pregnancy had in initiating her visual symptoms is difficult to estimate. These symptoms appeared during the seventh month of her pregnancy, and it seems fair to assume that during this time the pituitary gland, like the thyroid, showed physiologic enlargement.

CASE 9.—*Death of a mother harboring a cerebral tumor who had been delivered, by cesarean section, of a normal baby six weeks prematurely.*

E. E., a married woman aged 28, first came under observation on Dec. 18, 1942, at the suggestion of Dr. R. C. Thompson of Whittier, Calif. At this time she was about five months pregnant, with her first baby. For the previous year she had been subject to "sick headaches," which came at intervals of about three weeks and usually lasted from two to three days. The pain soon settled in the right side of her head and was described as constant and nagging.

Episodes of weakness and numbness of the right arm and hand appeared. At times her right hand became so limp that she could not move the fingers. At other times the right hand would "pull up and swing back and forth." She was right handed. On occasion, numbness of the right side of the face preceded the numbness in the right hand and arm. During the attacks, she had difficulty in speaking, knowing what she wished to say but being unable to say it.

On examination, she appeared alert and healthy. The enlarged uterus reached to the level of the umbilicus. The general physical examination was otherwise noncontributory. Her blood pressure was 110 systolic and 70 diastolic. Neurologic examination revealed nothing abnormal except for choking of both disks. There were embedding of both arteries and veins and measurable elevation of 3 D. of edema.

The Wassermann reaction of the blood was negative. The urine was normal.

Roentgenograms of the skull showed a normal condition except for thinning of the posterior clinoid processes of a normal-sized sella turcica and unusual

enlargement of one vascular marking on the left side of the skull, running from the posterior parietal to the occiptal region.

From these findings, there seemed to be little doubt that this young, five months pregnant woman had a cerebral tumor. The balance of evidence pointed to a tumor of the left cerebral hemisphere. The nature of the growth was not clear, but at the time we suspected it to be a meningioma.

What to do was the question. Should a craniotomy be performed at once? Should she be observed in the hope that her pregnancy would go to term and she would deliver the baby? Should an abortion be induced at this rather late stage of her pregnancy? She expressed a strong desire of having a child, as this was her first pregnancy after several years of marriage. After weighing the matter carefully, we decided to "watch and wait," possibly a wrong decision, as matters were to prove later. We were well aware of the time-honored axiom that the life of the mother is considered more important than that of her unborn child.

During the ensuing months, things progressed quietly. She had periodic attacks of pain, chiefly in the right side of the head, accompanied with nausea and vomiting. During these spells her vision was blurred. On one occasion her right hand became temporarily numb. The choking of the disks remained unchanged, and the pregnancy progressed normally, without any unusual symptoms. The blood pressure was 110 systolic and 80 diastolic.

During February 1942, in the seventh month of her pregnancy, her condition became more critical. She experienced frequent pain, which radiated from the back of her neck over the right side of her head. Headache was a daily occurrence. She now complained of periodic numbness of both hands and feet and was kept in bed. The neurologic examination revealed little except the choking of the disks, which by now had reached the stage of a long-standing process. Her vision was blurred much of the time, but the charted visual fields showed little contraction. The blindspots were enlarged to about four times their normal size: On February 4, vision was 20/30 in each eye.

Toward the end of February 1942, her headaches increased in severity, and uncontrolled tremors of the entire body set in. On February 27 a spell of unconsciousness occurred, which lasted all day. On March 5 she again became unconscious for four hours, after which she seemed confused and complained of numbness of both hands and feet. On the evening of March 9 her eyes protruded, "as in early exophthalmic goiter."

She was delivered of a living baby weighing 6 pounds 4 ounces (2,835 Gm.), by cesarean section, on March 10, by Dr. Thompson. Her general condition was described as satisfactory after the surgical procedure, but about four hours later she "suddenly stopped breathing." Artificial respiration was useless, and the patient died. Permission for autopsy was denied.

Comment.—Six years have elapsed since this tragic event, and I (C. W. R.) have pondered the pros and cons of the case again and again. Unfortunately, the type of brain tumor present could not be verified. That she had such a lesion seems undoubted. Its exact location could not have been determined without ventriculography. Its successful removal, in case of a glioma of almost any type, is improbable. How much the existing pregnancy would have added to the risk of an intracranial operation is difficult to answer. Had the tumor been a meningioma, the prospects of its successful removal would have been much better.

CASE 10.—*A woman aged 42 had had a decompression for supposed tumor of the brain thirteen years previously, with notable relief. A pseudotumor was diagnosed tentatively. The patient has been twice pregnant since operation.*

Mrs. C. D., aged 29, a Mexican housewife, was referred by Dr. F. E. Clough, of San Bernardino, Calif., on Jan. 28, 1935. She complained of severe headaches

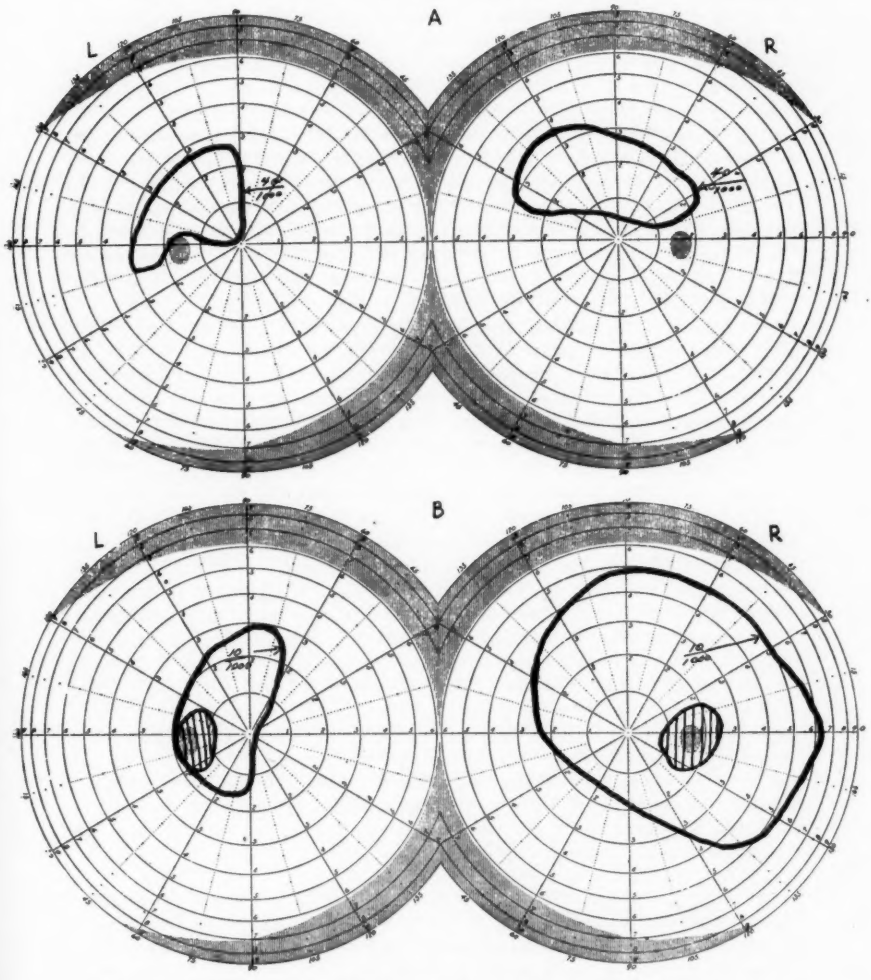

Fig. 13 (case 10).—*A*, marked contraction of the visual fields in a case of suspected "pseudotumor," taken just before operation (Jan. 28, 1935). Vision, without correction, was 20/20 in the right eye and the patient saw the card as "a little white spot" at 20 feet (6 meters) with the left eye.

B, visual fields taken thirteen years later (Feb. 9, 1948). Vision was 20/70 in the left eye and 20/20—3 in the right eye without correction.

during the previous two weeks. These were occiptal and were accompanied with nausea, vomiting and dizziness. There had been ringing in the right ear for two weeks. Her vision had become disturbed ten days previously and had failed so rapidly that she could no longer read. The left eye was more affected than the right.

She gave no history of previous injury. She had married at the age of 15 and had had 7 living children and 1 miscarriage, all prior to the appearance of her present symptoms. Examination showed suboccipital tenderness, greater on the left side than on the right. The optic fundi showed choking of both disks to an elevation of about 5 D. There were deep embedding of both arteries and veins and numerous long-standing exudates. The disks themselves were entirely obscured. The left pupil was slightly larger than the right. Both pupils reacted very poorly to light but well in accommodation. There was marked limitation of lateral gaze, both to the right and to the left. She could not turn the left eye beyond the midline but could turn the right eye outward to 30 degrees. Convergence was entirely lacking. There was considerable constriction of the visual fields; otherwise, the neurologic status was normal. The roentgenograms of the skull revealed nothing abnormal. The Wassermann reaction of the blood was negative. The visual fields showed marked contraction (fig. 13 *A*).

On Jan. 30, 1935, ventriculographic examination was unsuccessfully attempted. The right ventricle seemed to be collapsed. The left lateral ventricle was not tapped. A decompression was then carried out in the right subtemporal region. To our surprise, the patient showed remarkable improvement. Her headaches and vomiting stopped. The choking of the disks disappeared, and secondary atrophic changes set in. She then disappeared from sight for almost thirteen years.

She was next seen on Feb. 9, 1948, at which time it was learned that she was two months pregnant. Three years ago she had given birth to her eighth living child. The pregnancy and labor were normal. She now returned because her physician questioned whether, in view of her past history, she should continue with her present pregnancy.

Her general condition was excellent. The former operative wound was well healed, and there was no bulging of the decompressed area. Roentgenograms showed a normal sella turcica, no unusual intracranial densities or erosions and a well healed area of decompression in the right temporal region. Her eyegrounds showed sharply outlined, very pale disks, with new tissue in each optic cup. The veins were of average size, the arteries very small. The extraocular movements were normal in all respects. The visual fields showed less contraction than when we had first examined her, thirteen years before (fig. 13 *B*). Her neurologic status was otherwise normal. She stated that she still had headaches at times but that these were not severe. She had passed through her pregnancy three years previously without incident. It was thought that she could proceed with her present pregnancy.

Comment.—This case is unique in our experience and possibly should be classified under the heading of "pseudotumor." Nolen has discussed 2 cases of pregnancy in women with so-called pseudotumors. Certainly, a free interval of thirteen years is a long time for a cerebral tumor of any type to remain quiescent. Two facts seem indisputable: (*a*) She had fully developed signs of increased intracranial pressure in 1935, and (*b*) all signs of increased pressure had disappeared in 1948.

CASE 11.—*Cerebellar malformation; old chronic inflammatory process resembling cerebellar tumor at the age of 7 years; cesarean delivery of a normal child at the age of 24.*

On July 23, 1929, D. A., a 7 year old girl, was first examined because of occasional headache and unsteadiness in walking. Her birth had been a difficult breech presentation, but nothing amiss was noted at the time. There were several minor head injuries at the ages of 6 months, 3 years and 6 years, respectively, but none of them seemed in any way contributory to her symptoms. Her father, a physician, had died of a tumor of the brain.

As early as 2 years of age, it was noticed that she was not sure of herself on her feet. During the next five years the unsteadiness of gait increased. She tripped easily, staggered from side to side and could not run or walk straight. Her hands were unsteady to the point that writing was difficult. Two months before my first examination she had a severe headache. This was repeated two weeks before she was seen. There was no nausea or vomiting.

Examination revealed a sturdy girl of 7 years with a rather large head, measuring 58.5 cm. in circumference. The percussion note over the calvaria was definitely high pitched. The eyegrounds showed obliteration of the margins of the disks, with overfilling, and a tendency to embedding, of the vessels and elevation of about 1 D. She had no nystagmus. There was pronounced ataxia of both upper and lower extremities. She could not stand in Romberg's position, and her gait was unsteady and tottering. She went about the room holding onto objects. All the deep reflexes were equally increased, and on a few occasions clonic ankle jerks were obtained on each side. Babinski's response was equivocal bilaterally.

Roentgenograms of the skull showed pronounced convolutional atrophy with considerable absorption of the lime salts in various areas. The sella turcica was not eroded but appeared moderately enlarged.

A presumed diagnosis of cerebellar tumor was made, and operation was performed by Dr. Harvey Cushing on Oct. 14, 1929. A letter from him, dated Dec. 21, 1931, stated: "She had a most peculiar lesion with an enormous bulging of the vermis, which was tied down by adhesions to the front part of the spinal cord. I finally got this all free and found a foramen of Magendie big enough to put your finger into. I presume it was an old chronic inflammatory process, or possibly a malformation."

By April 4, 1935, six years after her operation, she was free from headaches. Her unsteadiness of gait was unchanged. The eyegrounds, now flat, showed the typical pallor of secondary optic nerve atrophy. Her head measured 59 cm. in circumference. The ataxia affected both the upper and the lower extremities, and she could not stand in the Romberg position. She held the head tipped toward the right most of the time. She was bright and alert, and was in class B of the sixth grade at school (about normal for a 13 year old child).

She was next seen on Oct. 8, 1940, when she was 18 years old. Her head now measured 60 cm. in diameter. The optic disks showed mild changes, suggesting secondary optic nerve atrophy. Her arms and hands were steadier than before, and she performed the finger to nose and finger to finger tests well, exhibiting a fine tremor of both hands at the end of the act. She stood quite steadily in Romberg's position. Her gait had become spastic, rather than ataxic, and she tended to walk on her toes. The knee jerks had become exceedingly lively, with an equivocal Babinski sign on the left. She was free from headaches and was alert mentally.

She next came to my attention on Nov. 8, 1946, when she was 24 years old. She had recently married and was three months pregnant. Her head measured 60 cm. in circumference. The percussion note over the calvaria was "a little high."

Her operative wound of Oct. 14, 1929 showed no elevation of the cerebellar flaps and no sign of increased pressure. Her eyegrounds were flat but showed "long-standing secondary changes." Her gait was definitely ataxic and spastic, although she could stand in Romberg's position.

The problem arose as to whether the pregnancy should be allowed to proceed. It was decided to do so, provided that untoward symptoms did not develop. It was agreed that she should be delivered by cesarean section. The pregnancy progressed normally, and she was delivered of a normal female child by cesarean section on April 4, 1947, by her physician, Dr. Irving Ress. A hysterectomy was then performed. She had no postpartum complications.

Comment.—In retrospect, it is unlikely that this girl ever had a cerebral tumor. Cushing's impression of "an old chronic inflammatory process, or possibly a malformation" was probably correct. However, both of us thought she had a cerebellar tumor before operation. In view of her great spasticity, the decision of Dr. Ress to perform a cesarean section and sterilize her after delivery was amply justified.

CASE 12.—*Evacuation of a subarachnoid cyst in the left motor face area of a pregnant woman. Cessation of jacksonian convulsions and spontaneous normal delivery after operation.*

E. S., a Caucasian woman aged 33, was admitted to the Los Angeles County Hospital on Oct. 16, 1943, in convulsions. The convulsions had started eleven days previously and, in spite of heroic measures in the way of dehydration and sedation, had continued. At that time she was estimated to be seven months pregnant. From relatives it was learned that she had been subject to convulsions since she was 21 and had been considered to be "epileptic" by her physician. At the age of 11 she had fallen on her head from a tree, this accident being considered a possible cause of her attacks. In spite of her convulsions, she had passed normally through two previous pregnancies.

Her condition on entry to the hospital became very critical and her attacks were purely of a jacksonian character (right side). They always started with twitching of the right side of the mouth and face. They then became generalized. During her lucid moments there were times when she was unable to speak. No objective motor weakness was anywhere made out. The attacks continued with increasing frequency and severity for four days, when it was decided to explore the left motor area of the brain in order to determine what was causing irritation of the face area.

The Wassermann reaction of the blood was negative. The spinal fluid showed an initial pressure of 225 mm., contained 9 cells and gave negative reactions to the Pandy and Wassermann tests. The urine showed a specific gravity of 1.018, gave negative reactions for albumin and sugar and gave 3 plus reaction for acetone.

On Oct. 20, 1943, an exploratory craniotomy was carried out on the left side. A puckered cortical scar was seen in what was presumed to be the face area. A moderate-sized cortical artery was found to be retracted under the surface of the brain at this point. When the artery was liberated and the sulcus spread, a cyst containing xanthochromic fluid was encountered. The overlying arachnoidal adhesions were freed, and the cyst, containing 5 cc. of yellow fluid, was emptied.

The postoperative course was stormy; but after six days the patient began to improve, and twenty-two days after operation it was felt that she was well enough to go home, as her convulsions had stopped and she was ambulatory. However, labor set in, and on November 12 she was delivered spontaneously of a 5 pound

2 ounce (2,325 Gm.) healthy baby girl. She has been followed for the past five years. Her convulsions have returned but are largely kept under control by medical treatment.

Comment.—This case is not included as one of a brain tumor. The subarachnoid cyst in the left motor strip apparently acted as a trigger point to set off the jacksonian attacks. A tumor in the same location might have done the same. Evacuation of the cyst stopped her attacks for the time being and allowed labor to proceed normally. It is debatable whether her convulsions were post-traumatic, consequent to falling on her head from a tree at the age of 11, or whether they were due to idiopathic epilepsy. One would hardly expect to find a circumscribed arachnoid cyst if the latter were true.

REVIEW OF THE LITERATURE

It seems an oversight that even in standard treatises of obstetrics and neurosurgery more attention has not been paid to tumors of the brain as a complicating factor in pregnancy. Many cases must have occurred that have not been reported. All authors are agreed that the situation thus produced gives rise to the suspicion of toxemia of pregnancy. It is not strange that other conditions, such as cerebral abscess, meningitis or conglomerate tubercle of the brain, have sometimes been mistaken for a tumor of the brain. In fact, cases of suspected cerebral tumor have been reported in which autopsy failed to reveal such a lesion, thus leading to the diagnosis of "pseudo tumor cerebri."

Nolen [3] reported the case of a 40 year old woman who, having borne eleven healthy children and remained well during these pregnancies, had right hemiplegia, left-sided headaches, tremors in her paretic right hand and oculomotor paralysis during her twelfth pregnancy. She recovered entirely a few weeks after delivery. She aborted during her thirteenth pregnancy, without development of neurologic symptoms, but during the second half of her fourteenth pregnancy she again manifested the same disorders as had appeared during her twelfth pregnancy. An artificial delivery by section was carried out because in her unconscious condition aspiration pneumonia had developed. She recovered a few months later and was reported to be in good health ten years after the first cerebral symptoms had appeared.

Nolen was at a loss for an explanation and considered the possibility of brain tumor or hydrocephalus, as well as intoxication, but was unable to arrive at an exact diagnosis. He stated that he had never known pregnancy to lead to hydrocephalus. He recited the case of a woman

3. Nolen, W.: Ein Fall von zuerst in der Schwangerschaft aufgetretenem und in zwei nach folgenden Schwangerschaften jedesmal rezidivierenden "Pseudo-Tumor cerebri," Berl. Klin. Wchnschr. **46**:2177-2180; 2240-2250, 1909.

reported by Oppenheim [4] in whom hydrocephalus was said to have developed twice during pregnancy and who died after her third delivery. Autopsy revealed chronic internal hydrocephalus, hydrops of the spinal medulla, chronic pachymeningitis and arachnitis with adhesions. Apparently, the cause of the hydrocephalus was not determined, unless the condition was secondary to a previous inflammatory condition of the brain which had led to adhesions and had obstructed the cerebrospinal fluid pathways. A brain tumor was not found. Nonne [5] was apparently the first to coin the term "pseudo tumor cerebri" to characterize the uncertain etiology in these obscure cases. He admitted that at the height of the disease the symptoms suggested intracranial tumor but expressed the belief that the long years of remission pointed against this assumption. However, Oppenheim concluded, after observing several cases for long periods, that in some way hydrocephalus played a part in these obscure cases. Bernard [6] (1899) reported a glioma the size of a hazelnut in the right optic tract of a woman five months pregnant, who died eighteen days after the appearance of left hemiplegia. Jacobi [7] cited a striking case of a woman who had a cystic tumor the size of a chestnut in the left temporal lobe and died in the third month of pregnancy.

Bernard's second case (1898) is of peculiar interest inasmuch as it is the only instance of cholesteatoma of the brain encountered in the literature. A 26 year old woman (bipara) had had cramps as a child. Her first pregnancy was accompanied with convulsions, with loss of consciousness and biting of the tongue one day after delivery. In the course of her second pregnancy she had severe headaches and jacksonian convulsions on the left side. These chiefly affected the face, although the left arm and leg at times participated in an attack. She became worse as the day of her delivery approached and passed into coma on the fifth day of labor. The clinical picture was that of high blood pressure, without albuminuria or generalized edema. The author expressed the opinion that she had an obscure organic process in the brain, the exact localization of which was impossible. She died sixty hours after delivery of a living full term child by anterior hysterectomy. At autopsy, a cholesteatoma the size of an apple was observed in the right cerebral

4. Oppenheim, H.: Ueber einen Fall von erworbenem idiopathischen Hydrocephalus internus, Charité-Ann. **15**:307-324, 1890.

5. Nonne, M.: Ueber Fälle vom Symptomkomplex "Tumor cerebri" mit Ausgang in Heilung (Pseudo Tumor cerebri): Ueber letal verlaufene Fälle von "Pseudotumor cerebri" mit Sektionsbefund, Deutsche Ztschr. f. Nervenh. **27**:169-216 (Nov. 9) 1904; Ueber Fälle von benignen Hirnhauttumoren: Ueber atypisch verlaufene Fälle von Hirnabszess sowie weitere klinische und anatomische Beiträge zur Frage vom "Pseudotumor cerebri," ibid. **33**:317-355 (Nov. 30) 1907.

6. Bernard, H.: Gehirnsarkom mit rapider Entwicklung während der Schwangerschaft und des Wochenbetts, Zentralbl. f. Gynäk. **23**:788, 1899; Sarcome cérébral á evolution rapide au cours de la grossesse et pendant les suites de couches, Bull. Soc. d'obst. Paris **1**:296-298, 1898.

7. Jacobi, W.: Hirntumor und Schwangerschaft, Psychiat.-neurol. Wchnschr. **23**:237-239, 1921-1922.

hemisphere, with extension into the anterior horn of the lateral ventricle. Bernard stated that cholesteatoma is a rare lesion, appearing in the vascular pia or the choroid plexus. Its site of predilection is in the neighborhood of the pons, medulla or cerebellum, although it is occasionally seen between the olfactory bulbs or the corpora quadrigemina. In the absence of choked disk or localizing symptoms, the diagnosis may become difficult and complicated. This is especially true when one takes into consideration epileptic convulsions and comatose conditions occurring during pregnancy—in other words, eclampsia. He stated that epileptic convulsions in themselves are pathognomonic of neither eclampsia nor brain tumor. Furthermore, albuminuria, oliguria and edema are not in themselves entirely characteristic of eclampsia. Finally, a rise in blood pressure in itself is not pathognomonic of brain tumor, as it also occurs in eclampsia. In the vast majority of cases of brain tumor complicating pregnancy, the first minor symptoms, such as headache and vomiting, cannot be distinguished from those due to the pregnant condition of the patient.

Bickenbach [8] considered the coincidence of a brain tumor during pregnancy as an unusual curiosity. He noted that only about 25 such cases had appeared in the literature, of which only a few had been described in detail. He stated that the clinical picture of brain tumor during pregnancy is not essentially different from that in nonpregnant women. However, the appearance of convulsions toward the end of pregnancy, or during delivery, creates a very difficult obstetric problem. He felt it extraordinary that women otherwise free from symptoms may show the clinical picture of brain tumor during pregnancy and that the symptoms may continue after pregnancy has passed. In handling such cases, the physician is concerned with the responsibility of more than a single life: the life of the mother and that of the unborn child. He stated the belief that the latter deserves the same consideration as the mother.

Fleischmann [9] raised the question whether or not clinical interruption of pregnancy is justifiable in cases of brain tumor. His case was that of a woman aged 25 whose first child was born Dec. 21, 1928. She was admitted to the hospital on Jan. 29, 1930, when she was about four months pregnant. At this time she showed choking of the right disk and beginning optic neuritis on the left. Roentgenograms showed enlargement of the sella turcica and increased convolutional markings on the convexity of the skull. On February 14 a diagnosis was made of tumor at the base of the brain, a little to the left of the midline. A large bone flap was turned in the left frontoparietal region, and, after an unsuccessful attempt to tap the ventricles, the wound was closed without a tumor being disclosed. Right hemiplegia developed, and on

8. Bickenbach, W.: Hirntumor und Schwangerschaft, Zentralbl. f. Gynäk. **53**:422-428 (Feb. 16), 1929.

9. Fleischmann, C.: Ist die kunstliche Unterbrechung der Schwangerschaft bei angeborenem erblichem Star oder bei Gehirntumor berechtigt? Zentralbl. f. Gynäk. **54**:1870-1873 (July 26) 1930.

March 3 high voltage roentgen therapy was instituted. Her symptoms improved; the choking of the disks receded, and on March 18 she gave birth to a living male child. She died on May 1, 1930. No mention is made of an autopsy, and apparently the presence of a tumor was not verified.

Fleischmann cited the following opinions expressed in the more recent literature concerning indications for the interruption of pregnancy in women who have brain tumors. Winter [10] stated the opinion that one does not interrupt pregnancy in cases of brain tumor, brain abscess or syphilis of the brain; only in hypophysial tumor may one perform abortion. In 1931 Winter [11] discussed the question of hypophysial tumor during pregnancy more fully and reported a case. His patient was a 22 year old bipara whose menarche began at 13 years of age and whose menses were always irregular, occurring at five to six week intervals and consisting of a three day painless flow. She first became pregnant at the age of 19, in 1928, and noticed rapidly failing vision during the fourth month of her pregnancy. Shortly thereafter the left eye became totally blind. In the seventh month of her pregnancy she was given high voltage roentgen therapy under the diagnosis of optic nerve atrophy, secondary to hypophysial tumor. She delivered normally at term, and the puerperium was uneventful. The left eye remained blind, and vision in the right eye was somewhat reduced. She next became pregnant in November 1930 and about six weeks later noticed failing vision in the right eye. Winter was convinced that during the interval there had developed bilateral optic nerve atrophy as a result of enlargement of the hypophysis. An interruption of the pregnancy was at once advised because of the threat of complete blindness. It was felt that the pregnant state tended to increase the hypophysial enlargement to the extent that irreparable damage would be done to the optic nerves. Consequently, at about the third month of pregnancy a hysterectomy was performed. This not only interrupted the pregnancy but sterilized the patient. Her vision immediately improved to the condition which had been present before she became pregnant for the second time, and was unchanged at the last examination, four months later. Winter showed two views of the sella turcica—the first, a normal sella, and the second, the patient's sella, showing its enlargement from pressure of the hypophysial tumor. Nolen asked whether changes occurring in the hypophysis during pregnancy could cause symptoms. Several authors

10. Winter, G.: Indikationen zur künstlichen Unterbrechung der Schwangerschaft, in Halban-Seitz: Biologie und Pathologie des Weibes, Berlin, Urban & Schwarzenberg, 1927, vol. 8, pt. 2, pp. 27-56.

11. Winter, E. W.: Hypophysentumor und Schwangerschaft, Arch. f. Gynäk. **147**:95-112, 1931.

have found swelling of the hypophysis during pregnancy. Comte [12] observed swelling of the hypophysis in 6 women who had died during pregnancy or shortly after delivery. There was consistent hyperplasia of the cells of the anterior lobe in all cases. Vejdovsky [13] reported the case of a woman with a tumor of the pituitary gland in whom headache and bitemporal hemianopsia developed during pregnancy. Roentgen radiation therapy stopped the headaches and improved her vision. She gave birth to a healthy child at term and remained well thereafter. One may question whether the tumor was a true adenoma of the hypophysis or simply physiologic enlargement of the gland during pregnancy. Winter [14] further stated that organic disease of the brain is rare and usually does not require the interruption of pregnancy. Novak [15] was noncommital, stating that the coincidence of cerebral tumor and pregnancy is purely accidental. During pregnancy the progress in cases of such a tumor is unfavorable, and the small number of recorded observations and the unpredictable progress of the disease do not allow one to decide. Krückmann,[16] an ophthalmologist, outlined the ophthalmologic indications for the interruption of pregnancy as follows: "In cases in which the ability to see in both eyes decreases strongly during a coincidental pregnancy, I am in favor of a prompt interruption of the pregnancy, particularly because during pregnancy the tumor tends to grow very rapidly." Fleischmann cited Stockel as expressing the opinion that one is legally permitted to interrupt a pregnancy only if the woman suffering from an ocular disease is approaching death or blindness, and then only if death or blindness can be prevented by the procedure. If a physician encounters a situation precisely as thus described—one which, fortunately, rarely occurs—he is confronted with a difficult decision. Not only must he act as attorney for the mother and her unborn child, but he must also heed the legal restrictions against him. From his practical experience he finds no support; from the literature, no advice. He then raises the question whether or not a test case could be created as an authoritative example in such exceptional situations. He suggests

12. Comte, L.: Contribution à l'étude de l'hypophyse humaine et de ses relations avec le corps thyroïde, Thèse de Lausanne, Jena, G. Fischer, 1898.

13. Vejdovsky, V.: Tumor of the Pituitary in Pregnancy, Časop, lék. česk. **64**:1504-1507 (Oct. 27) 1925.

14. Winter, G.: Die operative Geburtshilfe, in Halban-Seitz: Organische Gehirnerkrankungen, Biologie und Pathologie des Weibes, Berlin, Urban & Schwarzenberg, 1927, vol. 8, pt. 2, pp. 1-504.

15. Novak, J.: Beziehungen zwischen Nervensystem und Genitale, in Halban-Seitz, Kombination von Schwangerschaft und Hirntumoren, Biologie und Pathologie des Weibes, Berlin, Urban & Schwarzenberg, 1928, vol. 5, pt. 4, pp. 1369-1528.

16. Krückmann, E., in discussion, Centralbl. f. Gynäk. **53**:1250-1253, 1929; Ueber ophthalmologische Indikationen zur Unterbrechung der Schwangerschaft, Ztschr. f. Geburtsh u. Gynäk. **95**:340-348, 1929.

that the medical faculty of a recognized university, or a commission composed of physicians and a lawyer, might sit together in deliberation of the best course to pursue.

Isbruch [17] presented the case of a pregnant woman who had a tubercle of the brain, producing the clinical picture of a brain tumor. He stated that cerebral tubercles in childhood are not infrequent lesions and that Aschoff considered half the so-called brain tumors of childhood to be tubercles. The frequency of these lesions decreases as age advances; consequently, they are seldom seen in pregnant women. His case was presented as a problem both in differential diagnosis and in treatment. The patient, a 20 year old primipara, had vomited for the preceding eight weeks. The history revealed that she had previously been treated by aspiration for empyema on the right side and dry pleurisy on the left. She was believed to have been cured. During her first month of pregnancy she seldom vomited, but this symptom had increased during the preceding six weeks. Headache in the occipital and right frontal areas, often associated with dizziness, had appeared during the previous four weeks. On examination she was found to be between eight and nine months pregnant. The lungs were clear; the blood pressure was 120 systolic and 70 diastolic, and there was no edema of the soft tissues. The urine was normal except for slight sediment and an occasional epithelial cell and leukocyte. The Wassermann reaction of the blood was negative. A roentgenogram of the skull showed abnormal deepening of the sella turcica and convolutional impressions. Ophthalmoscopic examination revealed severe neuroretinitis with choking of the disks, which was greater on the right side than on the left.

A diagnosis of cerebellar tumor was made, and she was placed under medical treatment, consisting of repeated lumbar punctures, which were intended to lower the intracranial pressure. Her symptoms of headache, dizziness, nausea and vomiting increased. Bradycardia and suppression of urine also developed. In order to save the child, as well as the mother, it was deemed necessary to induce labor. After the birth of a premature female infant, 46 cm. in length, the mother's condition improved. On the third day post partum she had severe convulsions, of which she died. Postmortem examination of the brain revealed advanced internal hydrocephalus, which was secondary to a conglomerate cerebellar tubercle, somewhat larger than a walnut.

Isbruch then discussed the differential diagnosis of conglomerate tubercle of the brain and cerebral neoplasms, adding that brain tumors in a pregnant woman do not differ from those in nonpregnant persons. He added that the nervous system is often affected toward the end of

17. Isbruch, F. M.: Konglomerattuberkel im Kleinhirn unter dem Bilde eines Hirntumors während der Schwangerschaft, Med. Welt. **7**:198-199 (Feb. 11) 1933.

pregnancy, taking the form especially of "cerebropathic toxic gravida." An increase in spinal fluid pressure does not speak undeniably of brain tumor or against eclampsia, since in the latter condition edema of the brain often exists. This in itself may cause increase in spinal fluid pressure. The author advised "quick release," for the good both of the mother and of the child, in cases of cerebral neoplasm and conglomerate tubercle of the brain. He advised cesarean section if the mother is moribund and suggested that it even be done immediately post mortem.

Puccioni [18] reported the presence of a meningioma the shape of a mandarin which was observed at autopsy in the left cerebral hemisphere of a woman aged 42 who died after delivery by cesarean section.

Meade [19] cited the case of a 24 year old housewife who died in the seventh month of her pregnancy. She presented signs of headache, nausea, vomiting and papilledema, which were considered to represent toxic changes incident to her condition. She died suddenly after an intravenous injection of 50 per cent solution of dextrose, given to relieve headache. A living male infant was delivered by immediate postmortem cesarean section. Meade stressed that a living baby may be saved by immediate postmortem cesarean section, particularly if the mother is nontoxic. Autopsy revealed an "ependymal cyst of the choroid plexus."

Lukas [20] described the case of a primipara aged 30 who died suddenly four days after a normal pregnancy and delivery. At autopsy a large abscess was discovered in the right cerebellar lobe. It was thought to be secondary to old suppurative otitis media, which had been present four years previously.

Armstrong [21] reported the case of a woman with angiomatosis retinae (von Hippel's disease) who was delivered at term of a normal male infant by cesarean section. He stated that the case was not complicated by angiomatous cysts of the brain or spinal cord and that, accordingly, the condition could not be classified as Lindau's disease. He added that the case is the first recorded instance in which angiomatosis retinae has been accepted as an indication for cesarean section.

Emmert's [22] patient, a 28 year old multipara, died nine days after cesarean delivery of a living 8 pound 4 ounce (3,742 Gm.) baby girl.

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18. Puccioni, L.: Contributo chimico allo studio dei tumori cerebrali in gravidanza, Riv. ital. di ginec. **18** (supp.):690-710, 1935.

19. Meade, W. H.: Brain Tumor Complicating Pregnancy, J. Michigan M. Soc. **34**:293 (May) 1935.

20. Lukas, J.: Abscess of Cerebellum as Cause of Sudden Death During Puerperium, Časop. lék. česk. **75**:1124-1125 (Sept. 4) 1936.

21. Armstrong, M. V.: Angiomatosis Retinae (von Hippel's Disease, Lindau's Disease), Complicated by Pregnancy, Am. J. Obst. & Gynec. **34**:494-496 (Sept.) 1937.

22. Emmert, M.: Brain Tumor Complicating Pregnancy, Nebraska M. J. **22**:471-473 (Dec.) 1937.

Autopsy revealed a dark, semifluctuating tumor the size of a hen's egg, deep in the left parietal lobe. This tumor was considered to be metastatic, secondary to a flat, hairless mole on the anterior surface of the left forearm; this mole had undergone rapid growth and discoloration and had been removed eight months prior to the patient's death. The pathologist reported striking similarity between the metastatic brain tumor and the growth from her arm. Neither tumor showed any indication of pigment formation, and the cells were generally larger and more vascular than is usually seen in malignant melanomas. The final diagnosis was squamous cell carcinoma with metastasis to the brain.

Mann [23] stated that the coincidence of brain tumor and pregnancy is rare. His patient, a woman aged 24, was delivered of a living female child by cesarean section on Oct. 14, 1932. The child died on the following day. The mother vomited during the first three months of pregnancy and then quieted down until the sixth month. From then on she exhibited rapidly increasing signs of brain tumor. Approximately a month after her delivery, on November 12, Dr. Francis C. Grant performed a suboccipital craniotomy, discovering a deep-seated tumor in the left cerebellar lobe. Owing to the patient's poor condition, its removal was not attempted at that sitting. A recurrence of symptoms resulted in reexploration on May 25, 1933, when a medulloblastoma was removed from the left cerebellar hemisphere. In spite of three series of roentgen ray treatments, her condition continued to decline and she died in October 1936. Mann raised the question, "Shall pregnancy be terminated in cases complicated by brain tumor?" He did not find a unanimity of opinion in the literature.

Ospelt [24] observed the delivery of a woman who was ill with an oligodendroglioma of the brain. The first progressive symptoms had appeared in 1932. In October 1932, after the birth of her first child, strange sensations, occurring six or seven times a day and lasting several seconds, appeared in her right arm and leg. After delivery these difficulties gradually disappeared. Again, after the birth of her second child, in January 1934, she noticed the same sensations; at this time they were somewhat stronger. In June 1934 she experienced headache, failing vision, tinnitus, burning of the tongue and formication in the region of the mouth. On March 7, 1935 a diagnosis of cerebral tumor was made, and on March 23, 1935 trephination was carried out over the left cerebral hemisphere and a tumor the size of a hen's egg was removed from the upper end of the left sensory area of the brain. The tumor

23. Mann, B.: Brain Tumor Complicating Pregnancy, Am. J. Obst. & Gynec. **37**:1051-1052 (June) 1939.

24. Ospelt, M.: Glioma cerebri und Schwangerschaft, Zentralbl. f. Gynäk. **63**:1401-1405 (June 24) 1939.

proved to be an oligodendroglioma. After the surgical procedure a cerebrospinal fluid leak occurred and the fluid continued to drain. At first this complication was considered unfortunate, but in view of later events it was to be regarded as fortunate. The patient improved and was given high voltage roentgen ray treatments. In September 1937 she became pregnant for the third time. Because of rapid progression of symptoms, a second operation was performed on March 23, 1938. The tumor could not be radically removed, and, in spite of aphasia and a left hemiplegia, she was normally delivered of a lively baby girl on June 26, 1938. Ospelt went on to say that many deleterious effects from brain tumor have been described in cases in which a pregnant woman has gone into labor without the benefit of earlier trephination of the skull. In his patient, the cerebrospinal fluid leak prevented a sudden increase of intracranial pressure during childbirth. Hence, he made the following recommendations in treatment of pregnant women who have a complicating tumor of the brain. He at least advised emptying the ventricles when it is impossible to carry out a radical operation before labor. He appended the experience of others dealing with this complex problem.

Von Seuffert [25] reported a section in a woman who died of a gliosarcoma of the brain in the eighth month of her pregnancy. The asphyxiated twins thus delivered could not be revived. Cathala [26] succeeded in saving, by cesarean section, the life of the child of a woman who was dying of a glioma of the brain. Leisewitz [27] described a glioma which led to the death of the mother in the fourth month of pregnancy. Vogt's [28] patient died of a brain tumor in the fourth month of pregnancy. Decio [29] reported the death of a mother from a "sarcomatous glioma" of the cerebellum the size of a walnut, in the seventh month of her pregnancy. Hoehne [30] described a death during the second stage of labor from a glioma of the brain; a living child was secured by forceps delivery of the moribund mother. Martinetti's [31] patient displayed her first signs

25. von Seuffert, E.: Drei Fälle von Kaiserschnitt an der Toten, Arch. f. Gynäk. **82**:725-734, 1907.

26. Cathala, V.: Opération césarienne post mortem, Bull. Soc. d'obst. Paris **11**:144-150, 1908.

27. Leisewitz: Plötzliche Todesfälle von Wochnerinnen, Zentralbl. f. Gynäk. **33**:699 (May 15) 1909.

28. Vogt, E.: Gehirntumor in Wochenbett, Zentralbl. f. Gynäk. **42**:776, 1918.

29. Decio, C.: Tumore del cervalletto gravidanza, Riv. ital. di ginec. **3**:445 (May-June) 1925.

30. Hoehne, O.: Tod intra partum infolge von Kleinhirntumor, Zentralbl. f. Gynäk. **51**:2369-2371 (Sept. 10) 1927.

31. Martinetti, A.: Tumore cérébrale in puerpera confuso con embolia, Clin. ostet. **37**:216-221, 1935.

of trouble on the fifteenth puerperal day and died several days later of cerebral embolism.

In summary, Ospelt presented the following views: The gravid state produces a noxious influence on the brain tumor, tending to stimulate its growth. The fact that a brain tumor exists in the presence of pregnancy offers no contradiction, but rather an invitation, to operative procedure. If the tumor cannot be radically removed, even a trephination may produce a favorable influence on the course of labor. He stated that this is especially true when a cerebrospinal fluid leak exists, for such a valvular drainage can lower intracranial pressure. He admitted, however, that such a leak may produce an unfavorable influence on the pathologic process in the brain. Among other things, he stated the opinion that operation may prolong the life of the pregnant woman and increase the chances of viability of the fetus.

Duperrat [32] recently cited 2 instances in which the growth of a heretofore latent tumor or tubercle of the brain was hastened by pregnancy. His first patient, a woman aged 34, passed through a normal pregnancy and delivered on Jan. 13, 1937. The following day she complained of severe occipital headache. Examination revealed no motor, sensory or reflex changes, and there was no peculiar attitude of the head. On January 24 her pupils became fixed and examination of the fundi revealed recent retinal hemorrhages. She died suddenly eleven days after delivery. Autopsy revealed a voluminous *hemangio-reticulome* (hemangioblastoma?) of the left cerebellar hemisphere. Apparently, a tumor had not been suspected during the course of her pregnancy.

His second case concerned a multipara aged 34 who experienced a severe occipital headache the day after delivery. In spite of the absence of albuminuria or hypertension, these symptoms were interpreted as due to eclampsia. She held her head backward and to the right during her exacerbations of pain. A month later Clovis Vincent uncovered a tubercle of the vermis at operation.

Duperrat discussed what he termed the aggravating action of the gravid state on brain tumors. He stated the belief that at times pregnancy favors the growth of such tumors, while at other times and in different circumstances it tends to slow them down. Thus, he went on to state, one may imagine that after the gravid state and parturition there exists a vasomotor instability which, in a dramatic fashion and under the influence of divers factors, general or regional, known or unknown, may bring to light certain conditions, among which is brain tumor. He warned against always attributing convulsions occurring

32. Duperrat, B.: Tumeur cérébrale et grossesse, Presse méd. **53**:118-119 (March 10) 1945.

during pregnancy to eclampsia, for tumors of the brain may, and often do, cause convulsions. He further mentioned a personal communication of Bret, who observed a primipara aged 20 with a huge angioma of the face. This woman had had numerous convulsive attacks during the last months of her pregnancy. He stated the belief that it was logical to suppose that she also had an angioma of the brain, as such lesions frequently accompany trigeminal nevi of the face.

Alpers and Palmer [33] stated that brain tumor is a rare complication of pregnancy, and one difficult to differentiate from toxemia, especially if the latter is associated with choking of the disks. Their patient, a Negro woman aged 34, entered the Philadelphia General Hospital when she was three months pregnant. Vomiting appeared one month after conception and increased in frequency and intensity until her death, which occurred five days after her admission to the hospital. Before death, there developed extreme lethargy, drooping of the left upper eyelid and bilateral edema of the ankles. Autopsy did not reveal a cerebral tumor but showed punctate hemorrhages in the basal ganglia. Acute tubular nephritis and acute degeneration of the liver were also present. Clearly, this case was one of toxemia of pregnancy, but the development of choked disks strongly suggested the possibility of a tumor of the brain.

Bringle [34] described the uneventful delivery of a woman aged 27 with acromegaly from whom Sachs had removed a pituitary tumor four years previously. Before operation she had presented a typical picture of acromegaly, with bilateral primary optic nerve atrophy and bitemporal hemianopsia. Her periods, which had stopped nine months prior to operation, returned after removal of the tumor and a course of high voltage roentgen therapy. Throughout pregnancy, she had complained of headache, nausea, nervousness and crying spells. Extreme nervousness and weakness continued after delivery. The baby's condition was good. MacRae [35] reported the case of a pregnant woman aged 30 who died in convulsions as a result of a glioblastoma multiforme in the right frontal lobe. He stated that the fetal heart beat could be heard for thirty minutes after the mother's death, an observation which suggested to him that there would have been sufficient time to do a cesarean section post mortem and secure a living infant. He added that section was not considered "for obvious reasons," but did not state them.

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33. Alpers, B. J., and Palmer, H. D.: Cerebral and Spinal Complications of Pregnancy, J. Nerv. & Ment. Dis. **70**:465 (Nov.) 606 (Dec.) 1929.

34. Bringle, C. G.: Pregnancy in an Acromegalic Following Removal of a Pituitary Tumor, Memphis M. J. **12**:72-73 (May) 1937.

35. MacRae, K. S. E.: Survival of Fetus After Maternal Death Due to Intracranial Tumor, Brit. M. J. **1**:978-979 (May 13) 1939.

Perez, Dixon, Aranovich and Gori [36] presented the case of a woman aged 21 who died of a medulloblastoma of the cerebellum in her third month of pregnancy. Headaches and vomiting had been present for two and a half months. She had occasional muscular trembling of both arms and legs, which were clonic in character and came on after convulsions. The probability of toxicosis gravidarum was dismissed because the symptoms came surprisingly early in the course of her pregnancy. Neurologic examination pointed, rather, to a tumor of the brain. She died suddenly in convulsions. Necropsy showed the left cerebellar hemisphere, as well as the vermis, to be enlarged. A round tumor 4 cm. in diameter was found, which gave the histologic picture of medulloblastoma.

Chimenti [37] described the case of a woman aged 29 on whom cesarean section was performed in the eighth month of her pregnancy to save the mother and the child. This was accomplished, as the author stated, under an error in diagnosis. The symptoms of headache, nausea and vomiting, which had been considered manifestations of eclampsia during pregnancy, later proved to be due to a tumor of the cerebellopontile angle. This growth was subsequently removed, the patient surviving. The exact microscopic diagnosis of the tumor was not given.

Dieckmann [38] defined the toxemias of pregnancy as "a group of diseases which occur during pregnancy or the early puerperium, and are characterized by the appearance of one or more of the following signs: edema, proteinuria, hypertension, convulsions, or coma." He was speaking of the preeclamptic and eclamptic states. Contrary to many authors, he did not consider vomiting of pregnancy, as seen in hyperemesis gravidarum, as belonging to the toxemias.

Such symptoms appearing during pregnancy, however, must be given consideration if one has in mind the possibility of a complicating cerebral tumor. According to Shumann,[39] who included hyperemesis gravidarum as a true toxemia of early pregnancy, about 40 per cent of pregnant women show some signs of this condition, that is, nausea, vomiting, dehydration, acidosis and exhaustion. These symptoms, usually subsiding in the first trimester, may be present in patients with brain tumor. The coincidence is even truer in the preeclamptic and eclamptic states, during which the patient may have headache, dizziness, visual impairment, edema, progessive mental dulness and increasing irritability with

36. Perez, M. L.; Dixon, J.; Aranovich, J., and Gori, R.: Tumor cerebelar y embarazo, An. brasil. de ginec. **12**:271-279, 1941.

37. Chimenti, P.: A propósito de un error de diagnóstico (tumor ponto cerebeloso y vómitos incoercibles), An. d ateneo, Buenos Aires, 1945, pp. 213-217.

38. Dieckmann, W. J.: The Toxemias of Pregnancy, St. Louis, C. V. Mosby Company, 1941, pp. 21-44 and 224-235.

39. Shumann, E. A.: Textbook of Obstetrics, Philadelphia, W. B. Saunders Company, 1937, pp. 255-289.

focal and generalized convulsions. Generally speaking, true eclampsia occurs in 0.66 per cent of cases in the United States. Of this group, Shumann estimated that about 20 per cent of the mothers, and 20 to 30 per cent of the babies, die.

Arnold and Fay[40] became interested in the terminal stages of eclampsia. They found the brain to be edematous, with increased amounts of subarachnoid fluid. It was grayish white; the perivascular spaces were enlarged; punctate hemorrhages were frequent, and on occasion large focal or extensive subarachnoid hemorrhages occurred. In short, according to these authors, the eclamptic brain closely resembled the "wet brain" of cerebral edema.

The symptoms of headache, nausea, vomiting, stupor and convulsions, so frequently seen in eclampsia, may also be present with tumors of the brain. In eclampsia, cerebral edema seemed to be the most important factor. On trephining the brain in 3 cases of eclampsia during the acute convulsive state, Zangemeister[41] discovered marked cerebral edema, associated with increased amounts of subarachnoid fluid. Not all authors believe that cerebral edema is necessarily present in eclampsia. Cerebral edema, however, may exist without edema of the extremities.

It is now recognized that alteration in the fluid balance of the body constitutes one of the major changes in the toxemias of pregnancy. The pregnant patient has a positive water balance, which becomes exaggerated in toxemia and is indicative of sodium chloride retention. Dieckmann estimated that normal persons showed an average renal concentration of sodium chloride of 1.3 per cent, while that of normal pregnant women was 0.5 per cent and that of eclamptic patients only 0.185 per cent. Utilizing this knowledge, Torpin and Coppedge,[42] by forcing fluids and prescibing a salt-free diet, reduced the mortality to 12.8 per cent in a series of 350 women with eclampsia. Arnell,[43] using similar therapy, reported 142 consecutive cases of eclampsia without a maternal fatality. Electroencephalographic tracings were made on 26 of his patients. Abnormalities were found for only 3, an incidence coinciding with that for apparently normal persons. This would scarcely hold true had these patients had a brain tumor. An electroencephalogram should always be made if the patient is suspected of harboring a cerebral tumor.

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40. Arnold, J. D., and Fay, T.: Eclampsia: Its Prevention and Control by Means of Fluid Limitation and Dehydration, Surg. Gynec. & Obst. **55**:129-150 (Aug.) 1932.

41. Zangemeister, W.: Beitrag zur Auffassung und Behandlung der Eklampsie, Deutsche med. Wchnschr. **37**:1879-1881 (Oct. 12) 1911.

42. Torpin, R., and Coppedge: Eclampsia, South. M. J. **33**:673-681 (July) 1940.

43. Arnell, R. E.: A Therapeutic Regimen for Eclampsia, Am. J. Obst. & Gynec. **49**:1 and 49-80 (Jan.) 1945.

SUMMARY

In reviewing the data on our series of cases, we may divide them into (*a*) cases in which a brain tumor was verified microscopically; (*b*) cases in which the lesion was not verified microscopically but was almost certainly identified as a tumor by recovery of xanthochromic fluid from a cyst; or, in the case of the pituitary tumor, the diagnosis was strongly indicated by enlargement of the sella turcica; (*c*) cases in which the presence of a brain tumor was strongly probable, as shown by the clinical course, but the tumor was not identified at autopsy, and (*d*) cases in which the diagnosis of a brain tumor was suggested by the history but was later disproved as in the cases of "pseudo tumor cerebri," malformation of the cerebellum and cortical arachnoid cyst.

A. *Brain Tumor Verified Microscopically* (6 cases).—There were 4 proved cases of astrocytoma, in 3 of which both the mother and the baby died. In case 1 the outcome was inevitable, as the mother had an astrocytoma of the pons and died in the fifth month of her pregnancy. In case 2 the mother had an unsuspected astrocytoma of the left frontal lobe and died in the seventh month of her pregnancy. At autopsy the fetus was said to be in good condition, and it is possible that a living premature infant might have been saved by prompt postmortem cesarean section. This was not attempted. Case 3 was catastrophic in that it was recognized that the mother had a cerebellar tumor and operation for its relief had been scheduled. She died suddenly of hemorrhage into an astrocytoma of the left cerebellar hemisphere the day before that on which the operation was planned. At that time she was in her seventh month of pregnancy, with a viable fetus which might have been saved by prompt cesarean section, a procedure which was not performed. In case 7 the mother carried a cystic astrocytoma of the left cerebral hemisphere throughout her pregnancy. The fact that the cyst had been emptied, thus relieving pressure symptoms during her pregnancy, accounted for the fact that her pregnancy proceeded normally. However, the situation was fraught with danger, as shown by incomplete removal of an astrocytoma four months after delivery. Sterilization has been advised in this case, as another pregnancy would reopen the whole problem, and in a more serious form. Case 4 was a typical instance of an acoustic neurofibroma, on the right side, which apparently was unsuspected during the pregnancy. The pregnancy and delivery of a normal living infant were uneventful except that the patient had more nausea, vomiting and headache than should normally have been present. Her tumor was removed and the diagnosis verified, twenty-three days after the baby was born.

In the last case of a verified tumor (case 5) a meningioma of the sphenoidal ridge had been present during two pregnancies and deliveries.

The obstetric phase of the case offered no difficulties during the term of either pregnancy or delivery. It seemed significant, however, that during both her pregnancies the symptoms from the tumor were increased, possibly indicating that the neoplasm took on more rapid growth during those periods. On the other hand, it was probable that she had a disturbance in water balance, with increased tissue fluid, during her pregnancies due to retention of sodium, thus increasing cerebral edema.

While the case is not included in this series, it may be of interest to mention that we now have under observation a woman in her third month of pregnancy from whom a meningioma of the sphenoidal ridge was removed eight years ago. There is no indication of recurrence of the growth, and she is being allowed to proceed with her pregnancy.

B. *Brain Tumor Unverified Microscopically, But Almost Certainly Identified by Recovery of Cystic Fluid or Roentgenologic Findings* (2 cases).—In case 6, incomplete removal of a cystic tumor of the cerebellum was accomplished five years before the patient's pregnancy and delivery of a normal baby. The early part of her pregnancy was stormy, as a result of hyperemesis gravidarum. The cystic tumor contained xanthochromic fluid, and its emptying relieved her pressure symptoms. At the time of this report, eight years later, she again shows signs of recurrence of the growth, which we strongly suspect is a cystic astrocytoma. It is probable, therefore, that she had the tumor, and that it did not cause pressure symptoms, during her pregnancy.

Case 8 represents the only tumor of the pituitary in our series. While the tumor was not identified microscopically, the presence of an enlarged sella turcica, as well as bitemporal hemianoptic contraction, makes the diagnosis almost certain. It is believed that her chromophobe adenoma took on increased growth during her pregnancy, as her vision began to fail during the seventh month of gestation. Otherwise, things proceeded normally and she was delivered, now fourteen years ago, of a normal baby boy. High voltage roentgen radiation therapy has kept the growth under control during this period.

C. *Brain Tumor Strongly Probable as Judged from Clinical Course, but Diagnosis Unverified by Autopsy* (1 case).—Case 9 prompted the writing of this paper. The young woman presented unmistakable signs of increased intracranial pressure. It seemed probable that her tumor was in the left cerebral hemisphere. She was allowed to proceed with her pregnancy until within six weeks of term, when, because of alarming increase of symptoms, a cesarean section was performed. The baby lived, but the mother died a few hours after delivery and permission for autopsy was denied. Consequently, the diagnosis of brain tumor could not be verified. In retrospect, we feel that it might have been

wiser to have performed an exploratory craniotomy when she first came under observation, during the fifth month of her pregnancy. Even if the tumor could not have been removed, a decompression might have prolonged her life and lessened her suffering.

D. *Brain Tumor Suggested by History, but Later Disproved* (3 cases).—In case 10, an unlocalized brain tumor was suspected from the history and signs of increased intracranial pressure. It was not discovered at operation. A decompression has relieved her pressure symptoms for thirteen years. This is a long interval, and we are forced to believe that the lesion may have belonged in the class of "pseudo tumor cerebri." She has gone through one normal pregnancy since her operation, has had one miscarriage and is, at this writing, in the second month of a third postoperative pregnancy, which we are allowing to proceed.

In case 11 the lesion was not a brain tumor, but a malformation of the cerebellum with adhesions which blocked the foramens of Magendie and Luschka. The patient was operated on when 7 years old by Harvey Cushing. She became pregnant at the age of 24, at which time she was still spastic in all extremities and showed evidence of hydrocephalus. Her pregnancy was allowed to go to term, when a cesarean section resulted in a living child. A hysterectomy was immediately performed to prevent a repetition of pregnancy.

The convulsions in case 12 were due to an arachnoid cyst in the left motor face area. In this way it acted as a point of irritation to set off the jacksonian attacks on the right side. The cyst was probably traumatic in origin, representing the site of a former blood clot which had undergone cystic changes. Its removal stopped her convulsions for the time being. Later, however, the convulsive state returned.

Convulsions have properly been stressed as occurring frequently, in association both with toxemias of pregnancy and with brain tumors. In reviewing our material, we were surprised to find that they occurred in only 2 patients. None of the patients with verified tumors had convulsions. One patient (case 9) died in a terminal convulsive state after a cesarean section, and another (case 12) had jacksonian attacks on the right side, attributed to an arachnoid cyst in the left motor face area. In a larger series than ours, one would expect to find convulsions more frequently, for it has been well established that they occur in more than 30 per cent of patients with brain tumors.

Nausea and vomiting are frequently associated both with toxemias of pregnancy and with brain tumor. They were present in 3 cases of verified tumors: in case 2, with astrocytoma of the left frontal lobe; in case 3, with cystic astrocytoma of the left cerebellar hemisphere, and in case 4 with an acoustic neurofibroma on the right side. They also

occurred in 2 of the cases of unverified tumors: in case 6, with a cerebellar cyst, and in case 9, with an unidentified tumor, probably of the left cerebral hemisphere.

In all the cases in our series headache, in varying degree, was a symptom.

It is impossible to lay down any hard and fast rule for the conduct of the pregnant woman who has a brain tumor. Each case must be studied individually. Both the location and the type of tumor must be given consideration. It would seem that the course of patients with gliomas of one sort or another is much more rapid and fatal. In cases 1, 2 and 3, with astrocytomas of the pons, left frontal lobe and left cerebellar hemisphere, respectively, all the women died with their babies in utero. In none was there operative intervention. It is probable that the women with astrocytomas of the frontal lobe and left cerebellar hemisphere, respectively, might have been saved, together with their babies, if prompt surgical measures had been employed. At least, the lives of the mothers should have been prolonged and living babies delivered. Consequently, we believe that prompt operative intervention is indicated if the mother is suspected of having a glioma. We feel that there is greater cerebral edema surrounding a glioma than a benign tumor. The pregnant state probably tends even more to increase this edema.

Patients with a benign tumor may more safely wait, especially if their symptoms are not alarming. One of our patients with a meningioma of the sphenoidal ridge went through two pregnancies without incident; and 1 with an acoustic neurofibroma delivered normally. We feel that any surgical procedure on a pregnant woman increases her chances of abortion. It goes without saying that all such patients should be watched with the utmost care, so that surgical measures may be resorted to at short notice if it seems indicated.

We believe that the strain of labor increases intracranial pressure, although we have no exact figures to prove it. Certainly, straining from any other cause tends to raise intracranial pressure. We have consequently advised cesarean section as being safer than spontaneous delivery by normal channels for pregnant women harboring tumors of the brain.

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STUDIES ON HEADACHE

1. Effects of Carbon Dioxide–Oxygen Mixtures Given During Preheadache Phase of the Migraine Attack
2. Further Analysis of the Pain Mechanisms in Headache

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A LARGE body of clinical and experimental studies have illuminated some of the bodily changes which take place during an attack of migraine.[1] The pain of this headache is known to arise from dilated arteries either inside or outside the head or both. Certain of the preheadache phenomena have been studied and have been shown to be the result of cerebral vasoconstriction.

It is the purpose of this paper to describe further experiments which have been carried out in an attempt to clarify the nature of the vasoconstrictor and vasodilator phases of the attack.

EFFECTS OF CARBON DIOXIDE-OXYGEN MIXTURE GIVEN DURING PREHEADACHE (VASOCONSTRICTOR) STAGE

Certain of the preheadache phenomena have been shown to be the result of vasoconstriction in strategic areas of the brain or retina. A physician who had loss of segments of his visual fields prior to headache was able transiently to restore his vision to normal by inhalations of amyl nitrite, a powerful vasodilator substance.[2] As soon as the effects of the drug wore off the scotomas returned. During studies on decompression sickness in persons who had spontaneous attacks of migraine similar visual defects were noted. Electroencephalographic tracings made during the presence of such phenomena showed changes similar to those noted during periods of cerebral anoxemia.[3] Later, Engel, Ferris and Romano [4] found similar focal electroencephalographic changes arising

1. Wolff, H. G.: Headache and Other Head Pain, New York, Oxford University Press, 1948.

2. Schumacher, G., and Wolff, H. G.: Experimental Studies on Headache, Arch. Neurol. & Psychiat. **45**:199 (Feb.) 1941.

3. Engel, G. L.; Webb, J. P.; Ferris, E. B.; Romano, J.; Ryder, H., and Blankenhorn, M. A.: A Migraine-Like Syndrome Complicating Decompression Sickness, War Med. **5**:304, 1944.

4. Engel, G. L.; Ferris, E. B., and Romano, J.: Focal EEG Changes During Scotomas of Migraine, Am. J. M. Sc. **209**:650, 1945.

from the occipital pole opposite the side of the visual disturbance. When the visual disturbances subsided and were replaced by headache, the electroencephalographic tracing returned to normal. It is inferred that a similar mechanism underlies the speech defects, tinnitus and peripheral paresthesias which occasionally preceded headache, as well as those more generalized disturbances, such as sleepiness and uncontrollable yawning.

Dunning [5] examined a 24 year old woman whose migraine headaches for many years were preceded by paresthesias on one side of the body lasting approximately thirty minutes. On one occasion these preheadache phenomena, instead of subsiding and being followed by headache, progressed and persisted. She was left with hemiparesis and hemianesthesia, which remained for many months. These defects are believed to be the result of thrombosis of arteries following extreme spasm and circulatory stasis within strategic vessels during the vasoconstrictor stage of a migraine attack. Dunning [6] emphasized that thrombosis is the complication of the preheadache phase of vasoconstriction, while hemorrhage occurs during the vasodilatation phase, when headache is present.

In an attempt to study the vasoconstrictor phase further, a number of patients were given carbon dioxide by inhalation in the laboratory.[7] Carbon dioxide was used in these studies, primarily because it is known to exert a potent vasodilator influence on cerebral arteries. In their reactions to carbon dioxide, the cerebral vessels are sensitive, as well as prompt, and the magnitude of their response is great. All sizes of vessels in all parts of the brain respond to the drug.[8] Second, carbon dioxide itself does not produce headache, as does histamine administered intravenously. Third, carbon dioxide is a physiologic agent and appears to play an integral part in the normal vasoregulatory mechanism of the head. A fourth consideration in its selection is the important fact that it is simple to administer and is easy for the patient to accept.

Method.—Carbon dioxide in 10 per cent concentration was administered by face mask to recumbent patients for three periods of five minutes each. Five to fifteen minutes was allowed between trials to permit observation of the effects of the procedure and to allow the patient to rest after the exertion of the profound hyperventilation produced. The same technic was used in each experiment. If no effect was obtained after three trials, the procedure was discontinued. Mixtures of 10 per cent carbon dioxide in air and of 10 per cent carbon dioxide with 90 per cent oxygen were used in these experiments. The mixture used was not known to the patient. The pulse and blood pressure remained within the range of normal throughout all the trials.

5. Dunning, H. S.: Personal communication to the authors.

6. Dunning, H. S.: Intracranial and Extracranial Vascular Accidents in Migraine, Arch. Neurol. & Psychiat. **48**:396 (Sept.) 1942.

7. Marcussen, R. M., and Wolff, H. G.: Therapy of Migraine, J. A. M. A. **139**:198 (Jan. 22) 1949.

8. Wolff, H. G.: Cerebral Circulation, Physiol. Rev. **16**:4 and 575, 1936.

The carbon dioxide mixtures were administered during one of three phases of the migraine attack: during the vasoconstrictor stage, before the headache, during the interval when vasoconstrictor phenomena overlapped the painful, vasodilator phase, and when the headache alone was present.

Observations.—A total of 25 trials were carried out on 15 patients. In 5 instances only vasoconstrictor phenomena were present. In these, carbon dioxide–air mixtures produced transient clearing of the visual disturbances, with return of symptoms to their former intensity within five minutes after inhalation of the gas was discontinued. When the carbon dioxide–air combination was followed by the carbon dioxide–oxygen mixture in similar amounts or when the carbon dioxide–oxygen mixture was used alone, vision cleared completely and remained so. The expected headache did not follow.

One subject experienced extreme sleepiness and nausea as preheadache manifestations. Ordinarily these disappeared as the headache developed. During inhalation of the carbon dioxide–oxygen mixture the patient became alert; her nausea disappeared in less than the usual interval, and the expected headache did not follow. When headache was present, the results were so unpredictable that no conclusions could be drawn. Except in 1 subject, the headache was not increased by the procedure. On two occasions on which a 30 year old man inhaled the carbon dioxide–oxygen mixture in the setting of tension and fatigue at a time when he felt he might be getting a headache, a moderately severe headache developed and persisted for nearly thirty minutes after the inhalation was discontinued.

Comment.—From these experiments two inferences may be drawn: First, a powerful physiologic intracranial vasodilator, carbon dioxide, is effective in decreasing or abolishing the intracranial vasoconstrictor phenomena of the migraine attack. Second, oxygen when used in conjunction with carbon dioxide makes these effects more pronounced and may prevent the progression of the attack.

The effect of carbon dioxide–oxygen mixtures observed here is similar to, but more pronounced than, the effect of oxygen when used alone, as reported by others.[9] Furthermore, the effects on the preheadache phenomena are more predictable. The results as regards the termination of already existing headache were no more predictable than those reported by Alvarez. The latter[10] pointed out that the therapeutic effect in his series appeared to be better when oxygen was administered early in the attack. In his series, complete relief was noted in 42 per cent of patients with "apparently typical migraine" and 44 per cent were

9. Alvarez, W.: A New Treatment for Migraine, Proc. Staff Meet., Mayo Clin. **14**:173, 1939.

10. Alvarez, W., and Mason, A.: Results Obtained in Treatment of Headaches with Inhalation of Pure Oxygen, Proc. Staff Meet., Mayo Clin. **15**:616, 1940.

"helped." He found that 100 per cent oxygen had to be inhaled for periods ranging from fifteen to one hundred and twenty minutes to produce these effects.

The superiority of the combination of carbon dioxide and oxygen may rest on a dual effect. Inhalation of carbon dioxide in 10 per cent concentration alone was found to double the cerebral blood flow in one series.[11] Kety and Schmidt [12] reported that 5.7 per cent carbon dioxide produced a 75 per cent increase in blood flow as measured by the nitrous oxide technic. It is therefore postulated that the greatly increased amount of blood which is maximally saturated with oxygen corrects an underlying oxygen deficiency in a strategic area of the brain, where the neural impulses which set up the compensatory vascular dilatation of the migraine attack may originate. This postulation fits into the broader concept that the stage of painful vasodilatation is an attempt on the part of the organism to restore cranial circulatory homeostasis.

Although these experiments have not shown that the use of carbon dioxide–oxygen mixtures is entirely predictable, they indicate that the migraine attack can be interrupted before the headache develops. Further, they suggest that vasoconstriction is a constant feature of the type of attack studied and may persist into the period of painful vasodilatation.

A variety of vasodilators have been advocated in the therapy of migraine. Results have been varied and unpredictable, but in general it has been found that these substances are more likely to eliminate headache if used at the very onset of pain. That they have sometimes achieved this effect suggests that they operate in a manner similar to that proposed for carbon dioxide in these studies.

ANALYSIS OF PAIN MECHANISMS IN HEADACHE

OTHER OBSERVATIONS ON THE PREHEADACHE STATE

Kunkle [13] described a technic for measuring the amount of force necessary to produce threshold headache by sudden rotatory head jolt. This "jolt threshold" is low in persons with headache arising from intracranial blood vessels. It is also low in certain disturbed metabolic states, such as hypoglycemia, fever and "hang-over." There is no lowering of the jolt threshold in situations in which extracranial arteries alone are implicated.

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11. Gibbs, F. A.; Maxwell, H., and Gibbs, E. L.: Volume Flow of Blood Through the Human Brain, Arch. Neurol. & Psychiat. **57**:137 (Feb.) 1947.

12. Kety, S. S., and Schmidt, C. F.: Effects of Alterations in the Arterial Tension of Carbon Dioxide and Oxygen on Cerebral Blood Flow and Cerebral Oxygen Consumption of Normal Young Men, Federation Proc. **5**:55, 1946.

13. Kunkle, E. C.; Wolff, H. G.; Lund, D. W., and Maher, P. J.: Studies on Headache: Induced Mechanical Stresses in the Analysis of Headache Mechanisms, Tr. Am. Neurol. A. (1947) **72**:93, 1948.

When a normal person is inverted head down 60 degrees from the horizontal on a tilt table, there is transient dilatation of the arteries of the head, followed in thirty to sixty seconds by generalized cranial vasoconstriction, all without headache.[14] Trained subjects, such as certain circus performers who spend considerable time in the head-down position, experience no discomfort when they assume this position. After a prolonged period (two to three years) away from their work, these acrobats lose their ability to compensate rapidly and experience flushing, a sensation of fulness in the head and nasal obstruction when they begin to perform again. After a short reconditioning period, they quickly regain their ability to compensate rapidly. The fact that these compensatory mechanisms act so rapidly in highly trained subjects indicates that they are neurogenic.

Early vascular headache may be reduced or abolished as the vasoconstriction develops. The prompt response of the early migraine headache in the head-down position demonstrates that this early vasodilatation is modified by neurogenic factors, since it is overcome by an opposing reflex vasoconstrictor effect.[15] This fact may explain why a variety of circumstances, such as suggestion or a sudden outburst of feeling, may promptly and dramatically alter the course of a vascular headache or migraine attack.

EXPERIMENTAL INDUCTION OF HEADACHE BY ORDINARILY INNOCUOUS FACTORS

Headache was experimentally induced in subjects with moderate, though painless, cranial vasodilatation.

Observation.—A student aged 22, not ordinarily subject to headache, was participating in studies on cranial circulation in the head-down position. The previous evening he had consumed a considerable quantity of alcohol at a party. On the morning of the experiment he came to the laboratory feeling fatigued, mildly nauseated and with a low jolt threshold, but without headache. This was his usual reaction to drinking. Headache rarely accompanied his "hang-over."

When placed in the head-down position on the tilt table, this subject promptly had a moderately severe generalized headache. As the expected compensatory vasoconstriction appeared, the headache was reduced to about half its original intensity. It persisted until the subject was restored to the horizontal, at which time the pain was promptly eliminated.

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14. Marcussen, R. M., and Kunkle, E. C.: The Effect of the Head-Down Position on Cranial Circulation, to be published.

15. Wolff, H. G.; Marcussen, R. M., and Kunkle, E. C.: Studies on Headache: Analysis of the Contractile State of the Cranial Vascular Tree in Migraine, Tr. Am. Neurol. A. (1948) **73**:14, 1949.

Comment.—Circus acrobats who spent considerable periods in the head-down position had similar increase in headache on assuming the head-down position after the ingestion of alcohol.[14]

The onset of certain migraine headaches, presumably largely intracranial in origin, is preceded by a lowering of the jolt threshold. In some instances this lowered threshold lasts for several hours after such a headache has subsided, suggesting that the abnormal state of the vessel which lowers its pain threshold persists for some time before and after the stage of vasodilatation.

The nature of the underlying change in the cranial vessels which results in headache is unclear. It is evident, however, that dilatation and edema alone are insufficient for the production of pain from an artery, such as the temporal, which is known to be a source of headache. In certain circumstances the pain threshold is lowered in cranial vessels. This observation supports Pickering's [16] suggestion that, in addition to stretching of the vessel wall, there may be "another factor, such as sensitization of the pain nerve endings by a chemical agent," which leads to headache. When stress is added in the form of stretching the vessel walls by distention or dilatation, headache results. Experimental evidence suggests that increased blood flow and oxygenation of the brain interrupt the chain of events which would otherwise culminate in painful vasodilatation. Therefore it would appear that there are substances which affect the vascular reactivity of the cranial vessels, making them more responsive to vasodilator or vasoconstrictor agents, either chemical or neural. Shorr and his co-workers [17] have identified a vasodepressor material (ferrotin) and a vasoexcitor material which are capable of modifying the reactivity of blood vessel walls. The effect of these particular substances on the cranial vasculature is as yet unknown. They appear, however, only when tissue oxygen saturation is low.

FACTORS OTHER THAN ARTERIAL DILATATION INVOLVED IN PRODUCTION OF MIGRAINE HEADACHE

Clinical observation of the superficial arteries of the head, notably the temporal, during migraine headache involving the temporal regions has established that the artery on the painful side is enlarged, tender and often firmer to palpation. Compression of such an artery often diminished the intensity of the headache. The administration of ergotamine tartrate

16. Pickering, G. W.: Experimental Observations on Headache, Brit. M. J. **1**:907, 1939.

17. Shorr, E.; Zweifach, B. W.; Furchgott, R. F., and Baez, S.: Hepato-Renal Vasotropic Factors in Experimental Shock and Renal Hypertension, Tr. A. Am. Physicians **60**:28, 1947.

is followed by reduction or elimination of the headache, accompanied with a decrease in amplitude of pulsation of the vessel.[18]

In the course of study of a large number of migraine attacks, it was noted that the degree of visible distention or dilatation was not always proportional to the intensity of the headache. For example, in a man aged 50 there was moderate distention of the left temporal artery during headache in the left frontotemporal region, which began early in the morning. This headache subsided spontaneously during the day, but when the subject was seen again at 4 p.m. the diameter of the artery on the formerly painful side was greater than it had been during the headache. Similar variations were noted in other subjects. It is well known that many persons, including those prone to vascular headaches, may have marked cranial vasodilatation after exercise or after exposure to the sun, for example, without headache.

Experimental perfusion of cat ears with 0.5 mg. of acetylcholine bromide per hundred cubic centimeters of mammalian Ringer's solution produced edematous thickening of the vessel walls.[19] A somewhat similar experiment was performed on human subjects to evaluate the role of dilatation and edema in the production of headache. Iontophoretic application of methacholine, a powerful vasodilator, was used. This produced minimal trauma to the skin, while bringing the drug into contact with localized segments of the temporal artery.

Method.—A silver electrode with an area of 1 sq. cm. was covered with Canton flannel and fastened with adhesive tape over an exposed segment of the temporal artery. The electrode was saturated with 10 per cent methacholine chloride U. S. P. A galvanic current of 0.5 milliampere was provided by a simple iontophoresis appartus. The test electrode was attached to the positive pole. The negative electrode was a fabric cylinder soaked in isotonic sodium chloride solution and held in the subject's hand. Current was applied for periods ranging from five to thirty minutes.

Observations.—During the passage of current a tingling or low grade burning pain was usually experienced in the area beneath the positive electrode. After removal of the electrode, about half the subjects experienced a feeling of pressure over the ipsilateral temple. No systemic reactions to the agent were encountered with this technic.

The vessel itself responded in a predictable fashion. At the site of the electrode the vessel was visibly dilated. It felt thicker and firmer, and

18. Graham, J. R., and Wolff, H. G.: Mechanisms of Migraine Headache and Action of Ergotamine Tartrate, Arch. Neurol. & Psychiat. **39**:737 (April) 1938; A. Research. Nerve. & Ment. Dis., Proc. (1937) **18**:638, 1938.

19. Torda, C., and Wolff, H. G.: Experimental Studies on Headache: Transient Thickening of Walls of Cranial Arteries in Relation to Certain Phenomena of Migraine Headache and Action of Ergotamine Tartrate on Thickened Vessels, Arch. Neurol. & Psychiat. **53**:329 (May) 1945.

in at least 40 per cent of cases the amplitude of pulsation was significantly increased. The magnitude of the changes was roughly proportional to the amount of the agent introduced. However, there seemed to be no further change in the vessel after fifteen minutes. The findings after thirty minutes of iontophoresis were comparable to those produced after fifteen minutes. These vascular changes extended in the direction of blood flow for distances of 1 to 3 cm. When methacholine chloride was applied in a similar way to a vein on the inner aspect of the forearm, similar localized dilatation was observed. The changes in both vessels persisted as long as fifteen minutes.

In 60 trials on 11 subjects, the changes described were noted to a degree proportional to the amount of agent applied. In 1 subject, a woman who seldom experienced headache, a 2 plus aching pain was felt in the temporal region, centering about the site of the electrode, on several trials. In none of the other subjects were any painful sensations reported.

Subsequent elevation of the systemic blood pressure following vigorous physical exertion did not produce pain in the region of the involved segment of artery.

Neostigmine bromide was applied iontophoretically to the vessel before the methacholine in order to increase the local action of the vasodilator. This procedure produced no greater change in the vessel than methacholine alone, and no pain followed.

In a subject with a suitably exposed segment of temporal artery, approximately 5 cm. of the vessel was placed under the positive electrode. The resultant dilatation was in every way similar to that produced in the shorter segments and was likewise painless.

Histamine, applied in a like manner, similarly produced vasodilatation and edema of the vessel wall. There was no spontaneous pain from the involved segment and none after the production of a rise in systemic blood pressure by exercise.

Comment.—These experiments lead to the conclusion that vasodilatation, produced by the method described, which is often followed by local edema of the extracranial vessel walls, is in itself insufficient to produce pain. Furthermore, an increase in the systemic blood pressure, and thus an increase in the intramural pressure in the involved segment, is likewise painless.

Rapid and extreme increase in intravascular pressure in the arteries within the head will induce headache in most persons. Thus, on bladder distention in paraplegic patients with lesions above the sixth thoracic segment, a pressure response is evoked which is associated with severe headache. This is abolished by increasing the intracranial pressure, an effect demonstrating its intracranial origin. Also, the massaging of a

pheochromocytoma, with subsequent sudden elevation in blood pressure, is associated with severe headache. But these are extreme instances of vascular distention, and probably other factors facilitate the induction of headache in their absence. Indeed, such extreme vascular changes are not a part of the usual vascular headache attack.

From the experiments just described, one may postulate that, essential though the dilatation is, other changes in the state of the vessel are necessary for the production of pain with vasodilatation in the commoner vascular headache or migraine attack. It is postulated that, associated with the vasodilatation and edema which occur during the attack of headache, there is liberated locally an agent that lowers the pain threshold.

Probably there are other factors inherent in the individual case, for most persons do not have vascular headache except under such unusual stresses as fever.

FORMULATION OF THE MECHANISMS OF THE MIGRAINE ATTACK

A few of the physiologic steps by which the person translates a threat into a bodily disorder which compels him to retreat are recognized. Concerning others there are provocative hints. Unquestionably, there are others still unsuspected. Despite undoubted gaps in present knowledge, a train of events which comprise the "migraine attack" has been elucidated.

Early in the attack, perhaps days or hours before the headache phase, there appears to be a change in cranial vascular reactivity. Vasoconstriction is the next step, and this change may occur in a variety of locations inside the head. Most patients have no symptoms during this phase. In some, however, the vasoconstriction is manifest by scotomas, paresthesias and the like, while in others there is somnolence, thickened speech or yawning. By this time there has been a lowering of the pain threshold in the pain-sensitive arteries of the head, as manifested by a lowered jolt threshold. A final phase of the attack is vasodilatory. This may be a mechanism which is called into play to combat vasconstriction in order that the homeostasis of the cranial circulation may be restored. When such vasodilatation does occur in certain vessels whose pain threshold is lowered, headache results. This vasodilatation most frequently affects branches of the external carotid artery, but portions of the internal carotid system may be involved. The variety in distribution of vessels which may be involved explains the wide range of variations in the nature and location of vascular headache encountered.

SUMMARY AND CONCLUSIONS

The preheadache phenomena of migraine, visual disturbances, paresthesias and dysarthria are associated with, and probably due to,

cranial vasoconstriction. These phenomena can be modified or abolished by certain agents which produce cranial vasodilatation.

A series of patients were given a 10 per cent carbon dioxide–90 per cent oxygen mixture by face mask during the preheadache or early headache phase. This mixture abolished the preheadache phenomena and aborted the headache in most of the trials. Ten per cent carbon dioxide in air was less effective, having a shorter and more transient effect.

There was a lowering of the pain threshold in the intracranial vessels without headache in certain stressful circumstances. The "jolt threshold" was low before and after certain intracranial vascular headaches in a setting of stress and fatigue. After the ingestion of a moderate amount of alcohol, headache could be induced by inverting the subject 60 degrees from the horizontal.

Local vasodilatation of a segment of the temporal artery was produced by iontophoretic application of metacholine chloride and by histamine. Pain was not induced in 64 trials, even though pronounced vasodilatation and edema of the vessel wall were obtained. It is inferred therefore that, in addition to dilatation and edema, other factors are probably necessary for the production of vascular headache of the migraine type.

Certain of the chain of bodily changes leading to migraine headache are evident. Days or hours before the headache there is a change in vascular reactivity followed by vasoconstriction. This is followed by vasodilatation, which is painful, owing in part to a lowering of pain threshold in the vessels. The vasodilatation may be an attempt on the part of the body to restore the homeostasis of cranial circulation.

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STUDIES ON HEADACHE

Distention of the Rectum, Sigmoid Colon and Bladder as a Source of Headache in Intact Human Subjects

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CONSTIPATION and distention of the bladder are sometimes associated with headache, and Alvarez [1] and Donaldson [2] reported headache occurring with distention of the rectum with cotton tampons. It is the purpose of this study further to analyze the relation of headache and other effects that may be associated with prolonged distention of the large bowel or bladder.

METHOD

Seven volunteers, with ages ranging from 13 to 54 years, were selected for distention of the large bowel. Daily routine was interrupted only to administer cleansing enemas of saline solution. Approximately two hours after the noon meal a rubber balloon 17 cm. in length attached over a firm rubber tubing of 1 cm. diameter was inserted slowly and painlessly into the rectum. The distance of insertion into the large bowel varied from 20 to 40 cm. Distention of the rectum and sigmoid colon was then produced for one to one and a half hours by inflation with air, and an average balloon pressure of 25 mm. of mercury was indicated by means of an incorporated mercury manometer. The palpable balloon size varied from 8 by 26 cm. to 5 by 18 cm., and the position was easily palpable in the suprapubic region or in the left hypochondrium.

In most instances air was added intermittently during the experiment to compensate for the drop in pressure due to stretching and relaxation of the intestine. The subject remained supine throughout, and a constant feeling of "fulness" in the pelvis and an "urge to defecate" were experienced and maintained throughout the period of observation. The pulse, blood pressure, respiration, skin moisture and facial color were noted at ten minute intervals during the procedure. Preliminary and follow-up control observations were made with the uninflated balloon inserted into position.

Five volunteers, ranging in age from 35 to 50 years, without demonstrable neurologic disease, were selected for distention of the bladder. This was main-

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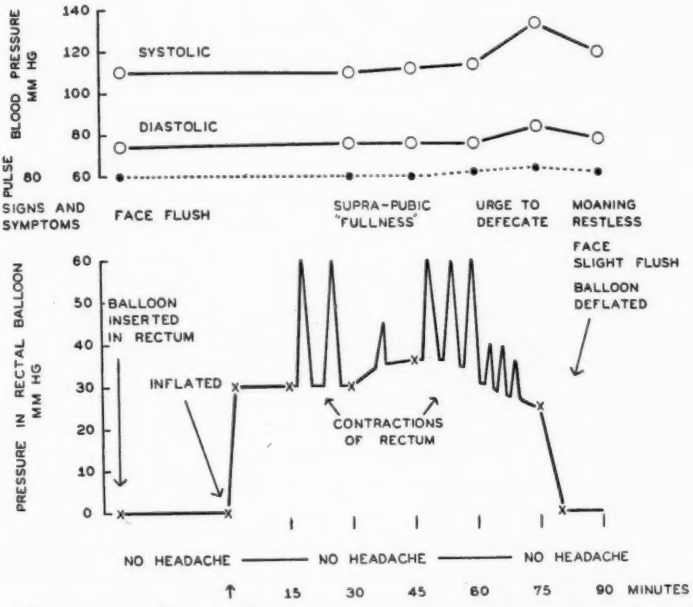
1. Alvarez, W.: The Syndrome of Mild Reverse Peristalsis, J. A. M. A. **69**:2018 (Dec. 15) 1917; Origin of So-Called Autointoxication Symptoms, ibid. **72**:8 (Jan. 4) 1919.

2. Donaldson, A. M.: Relation of Constipation to Intestinal Intoxication, J. A. M. A. **78**:884 (March 25) 1922.

tained for one hour by introducing sterile isotonic solution of sodium chloride through a retention catheter. Constant bladder pressure, recorded by an incorporated cystometer, ranged from 10 to 40 mm. of mercury, with a usual base line of 25 mm. of mercury. In all, the bladders were filled to the point of constant suprapubic "fullness" and "urge to urinate," and the retained volumes varied from 460 to 1,000 cc. Observations on pulse, respiration, blood pressure, sweating and color and temperature of the skin were noted at ten minute intervals during the experiment. The preliminary and follow-up control observations were made with the catheter in place.

RESULTS

Distention of the Large Bowel.—Group A, consisting of 5 subjects, gave no past history of constipation or headache. Group B, consisting



Effects of experimental distention of the rectum and sigmoid colon in a subject with a history of constipation. Although distention for seventy-five minutes was associated with considerable local discomfort, headache was not elicited.

of 2 subjects, gave a past history of constipation and of headache unassociated with constipation. With minimally uncomfortable distention, all 7 subjects experienced no headache or significant change in pulse, blood pressure, respiration, sweating or temperature or color of the skin. Throughout the procedure complaints of transient cramplike pains in the suprapubic area were seen to be associated with slow fluctuations of the balloon pressure from 20 to 60 mm. of mercury. It is inferred from this observation that increased stretch of the wall of the

large bowel results in discomfort, and secondarily in contractions, which sometimes occur in series. The latter induced momentary pain of high intensity and cramps, presumably due to further distortion of intramural pain endings. One person from each group was subjected for eight minutes to moderately painful rectal distention, and this led to simultaneous and transient elevation of 30 to 35 mm. of mercury in the systolic and diastolic blood pressures. Neither of these 2 subjects at this time had significant changes in his pulse, respiration, sweating or temperature or color of the skin. With partial deflation, pain in the pelvis ceased, and the blood pressure promptly returned to the control level. Typical observations are illustrated in the accompanying chart.

Distention of the Bladder.—Distention of the bladder was produced for an hour in each of 5 subjects. All experienced mild bladder discomfort, but this did not lead to headache or to significant changes in pulse, respiration, blood pressure, sweating or color or temperature of the skin. One subject had a 20 mm. rise in systolic blood pressure only during five minutes of moderate pain produced by further increase in the retained volume. There was only slight increase in bladder pressure, but no waves of contraction or markedly increased pressure were recorded. Headache was not noted.

COMMENT

Guttmann and Whitteridge [3] reported that sudden vesical and rectal distention for five to ten seconds in paraplegic patients with lesions above the fifth thoracic segment of the cord produced vasoconstriction of the fingers and toes, reduced the skin temperature sharply in the feet, elevated the pulse and produced a headache which was accompanied with a rise of 70 to 160 mm. of mercury in systolic blood pressure and a rise of 50 mm. of mercury in diastolic blood pressure. However, with lesions at or below the sixth thoracic segment there were the same fall in the temperature of the leg and the same decrease in pulse volume in the toes, but the blood flow increased in the fingers and the blood pressure did not rise more than 30 mm. of mercury.

Paroxysmal hypertension was also reported by Thompson and Witham [4] in cases of high lesions of the spinal cord when the bladder was distended in the course of cystometry. Head and Riddoch [5] reported

3. Guttmann, L., and Whitteridge, D.: Physiological Disturbances Produced by Distention of the Bladder, Proc. Roy. Soc. Med. **40**:229, 1946.

4. Thompson, C. E., and Witham, A. C.: Paroxysmal Hypertension in Spinal-Cord Injuries, New England J. Med. **239**:291, 1948.

5. Head, H., and Riddoch, G.: The Automatic Bladder, Excessive Sweating and Some Other Reflex Conditions, in Gross Injuries of the Spinal Cord, Brain **40**:188, 1917.

mass reflex sweating in paraplegic patients occurring from the noxious stimulus of an enema.

Schumacher and Guthrie [6] reported similar paroxysmal headache and hypertension from distention of the bladder and rectum with transections of the spinal cord above the eighth thoracic segment and were able to prevent or reduce headache by pressure on the common carotid artery, by lowering the systemic blood pressure with tetraethylammonium chloride or by increasing subarachnoid pressure by introducing saline solution at a pressure of 600 to 800 mm,, thereby supporting the painfully dilated intracranial arteries.

It is suggested that these vasomotor phenomena are a "mass sympathetic outflow" from an intact, large stump of spinal cord distal to a traumatic transection. The autonomic discharge is part of a "mass reflex" fired by noxious impulses from the bladder and rectum and is made possible by loss of suprasegmental inhibition of the segmental reflex arcs.

Our observations indicate that such autonomic discharges do not occur from distention of the large bowel or bladder in human subjects with intact segmental reflexes. During this study opportunity was available to dilate the sigmoid colon in a patient who had an ascending myelitis syndrome with a stationary level at the first thoracic dermatome, below which there was no sensation, deep reflexes, motility or sweating, indicating almost complete destruction of the cord below the first thoracic level. In this patient, one hour of distention of the sigmoid colon failed significantly to alter the pulse, respiration, sweating, blood pressure or color or temperature of the skin. Headache did not occur. This further suggests that the massive autonomic effects seen with traumatic transections of the cord depend on intact segmental reflexes in a large distal stump of the spinal cord.

SUMMARY

Headache did not result from experimental distention of the bladder or large bowel in human subjects with intact segmental reflexes. It is inferred that in normal human subjects with constipation or with urinary retention the mechanism of any associated headache is probably not directly related to the visceral distention or to contraction of the large bowel. Moreover, minimally painful distention of the bladder and large bowel in normal human subjects does not result in significant autonomic effects. It is probable, therefore, that the constipation and headache associated with it are not causally related to the distention.

525 East Sixty-Eighth Street (21).

6. Schumacher, G., and Guthrie, T. C.: Mechanism of Headache Induced by Distention of Bladder and Rectum in Patients with Spinal Cord Injuries, to be published.

EVALUATION OF ANTIEPILEPTIC DRUGS

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AND
CHARLES R. ENSOR, M.S.
DETROIT

TWO PRINCIPAL electric shock methods have been employed for the laboratory appraisal of anticonvulsant drugs: (*a*) the method of Putnam and Merritt [1] and (*b*) that of Toman, Swinyard and Goodman.[2] In the former, the anticonvulsant potency of a compound is determined by its ability to raise the electric shock convulsion threshold in the cat. Convulsions are produced in an animal by passing an intermittent current through the brain for ten seconds. The latter method differs from the former in that the abolition of the extensor tonic component of the convulsion is taken as a measure of anticonvulsant activity. In untreated animals given a threshold stimulus for 0.2 second the convulsion begins with flexion, followed by tonic extension of the hindlimbs and then usually by clonic movements. Rats or mice are commonly used in this test.

Opinions differ as to the merit of the two methods in the appraisal of potential antiepileptic drugs. The disparity is due partly to criticisms which are based on data obtained by one procedure only. In order to reach the most valid conclusion, it is essential, therefore, to determine the activities of anticonvulsant drugs by both methods and to compare the results with the clinical observations on their use in the treatment of epilepsy. The experiments to be reported in this paper were conducted with such a purpose in mind.

METHODS

A 60 cycle half-wave current from a 25Z5 vacuum tube rectifier was used to stimulate the cat. The strength of current was adjusted with a variable transformer. The experimental threshold of the animal was determined two and four hours, respectively, after oral administration of the drug. The drug was given once daily, and measurements of the convulsion threshold were made for three successive days. For each dose level 3 cats were employed; the average value of

1. Putnam, T. J., and Merritt, H. H.: Experimental Determination of the Anticonvulsant Properties of Some Phenyl Derivatives, Science **85**:525, 1937.

2. Toman, J. E. P.; Swinyard, E. A., and Goodman, L. S.: Properties of Maximal Seizures and Their Alteration by Anticonvulsant Drugs and Other Agents, J. Neurophysiol. **9**:231, 1946.

the increased convulsion thresholds was taken as an index of the anticonvulsant potency of a compound. Otherwise, the procedure and the rating system for anticonvulsant activity were essentially the same as those employed by Putnam and Merritt.

The supramaximal shock technic of Toman, Swinyard and Goodman was used to produce convulsions in rats and in mice.[3] The currents employed were 150 milliamperes for rats and 24 milliamperes for mice; these were about three times the normal threshold stimuli for these animals. The stimulus was applied to the rat with Spiegel corneal electrodes,[4] and to the mouse by clips attached to the two ears. The determination was made two hours after oral administration of a drug, a time which was found to give the maximal anticonvulsant effect of most compounds studied. The anticonvulsant activity of a compound is expressed in terms of the dose that would protect 50 per cent of the animals from the extensor component of the tonic phase. Thirty rats, 5 per dose, were used to obtain the dose-response relationship; the 50 per cent protective value was estimated graphically by the probit-dose method of Miller and Tainter.[5]

The following specifications were adhered to for the testing animals: healthy cats, which gave a control convulsion threshold of less than 20 milliamperes; male rats of the Sprague-Dawley strain weighing between 150 and 200 Gm., and albino male mice weighing around 25 Gm. Solid food was withdrawn from the cages eighteen to twenty-four hours prior to testing; in this period the cats were fed once daily with milk.

The drugs chosen for our study were diphenylhydantoin sodium U. S. P. (dilantin sodium®); 3-methyl-5, 5-phenylethylhydantoin (mesantoin®); 5,5-phenylethylhydantoin (nirvanol®); phenobarbital sodium U. S. P.; mephobarbital (N-methylphenylethyl barbituric acid; mebaral®); phenylacetylurea (phenurone®); carbromal N. F. (bromodiethylacetylurea); 5,5-diphenyl 2,4-dioxazolidenedione (epidon®), and trimethadione (3,5,5-trimethyloxazolidene-2,4-dione; tridione®). The insoluble compounds were finely suspended in 7 per cent acacia for oral administration.

In addition to being tested in electric shock convulsions, these compounds were tested against metrazol® (pentamethylenetetrazol) convulsions in the rat. The metrazol® solution, 93 mg. per kilogram of body weight (95 to 100 per cent of the convulsant dose), was injected subcutaneously one-half hour after the animal had been given perorally the drug to be tested. The anti-metrazol® rating is based on the number of the 5 rats that were protected from convulsions within thirty minutes after administration of metrazol®, a 4 plus rating indicating protection of 5 animals.

RESULTS AND COMMENT

The data in the accompanying table indicate that in nontoxic doses, expressed in milligrams per kilogram of body weight, diphenylhydantoin (dilantin®) is the most potent compound in raising the electric shock

3. The stimulator was supplied by the Hans-Tech Company of Salt Lake City.

4. Spiegel, E. A.: Quantitative Determination of the Convulsive Reactivity by Electrical Stimulation of the Brain with the Skull Intact, J. Lab. & Clin. Med. **22**:1274, 1937.

5. Miller, L. C., and Tainter, M. L.: Estimation of ED_{50} and Its Error by Means of Logarithmic-Probit Graph Paper, Proc. Soc. Exper. Biol. & Med. **57**:261, 1944.

Drug†	Electric Shock Convulsions*							"Anti-Metrazol" Convulsions			Clinical Results		
	Cat (P. M.)			Rat (T. S. G.)		Mouse (T. S. G.)							
	Dose, Mg./Kg. Orally	Toxic Signs‡	Rating	PD_{50} ± S. E.	Toxic Signs	PD_{50} ± S. E.	Toxic Signs	Dose, Mg./Kg., Orally	Toxic Signs	Rating	Grand Mal	Petit Mal	Psychomotor Equivalent
Diphenylhydantoin sodium.....	25	—	++++	24 ± 1.3	—	11.4± 0.5	—	500	Sl. dep.	—	++++	—	++
	12.5	—	+++					250	Sl. dep.	—			
"Mesantoin".....	50	Sl. dep.	++++	7.1± 0.6	—	45 ± 1.8	—	250	Sl. dep.	++++	++++	?	+
	25	—	+++					100	—	++			
"Nirvanol".....	50	Md. dep.	++++	14.2± 0.8	—	37.5± 1.5	—	500	Dp. dep.	++++		Too toxic	
	25	Sl. dep.	++					250	Sl. dep.	+++			
Phenobarbital.....	40	Md. dep.	++++	8.6± 0.2	—	23.6± 0.8	—	50	—	++++	+++	++	?
	25	Sl. dep.	++					25	—	++			
Mephobarbital ("mebaral").....	25	Md. dep.	++++	24 ± 5.0	—	35.5± 1.6	—	25	—	++++	++	++	?
	12.5	—	+					12.5	—	++			
"Phenurone".....	200	Dp. dep.	++++	20 ± 1.7	—	150 ±14	—	400	—	++++	++	++	++
	100	—	++					250	—	+++			
Carbromal.....	100	Excit.	+	40 ± 3.0	—	288 ± 9	—	25	—	++++	?	?	?
	50	—	—					16	—	+			
"Epidon".....	100	Sl. dep.	+++	452 ±27	—	660	—	500	Sl. dep.	+	++	?	?
	75	—	++										
Trimethadione ("tridione").....	500	Sl. dep.	+	560 ±19	Sl. dep.	980 ±33	Sl. dep.	250	—	++++	—	++++	—
	250	—	—					125	—	++			

* P. M. indicates the Putnam and Merritt method; T. S. G., the Toman, Swinyard and Goodman method.

† Trimethadione was supplied by Dr. M. A. Spielman, of Abbott Research Laboratories. The other compounds were made available to us by Dr. L. M. Long, Chemical Division, Research Laboratories, Parke, Davis & Company.

‡ Sl., Md. and Dp. dep. mean slight, moderate and deep depression.

threshold in the cat by the method of Putnam and Merritt. Mesantoin® appears next in potency, followed by nirvanol,® phenobarbital, mephobarbital, epidon,® phenurone,® carbromal and trimethadione. A similar order of activity is shown for these compounds when tested in mice by the supramaximal shock procedure of Toman, Swinyard and Goodman. In rats, on the other hand, mesantoin,® phenobarbital, nirvanol® and phenurone® give more protection of the extensor component of the convulsion than did phenylhydantoin, mephobarbital, carbromal, epidon® and trimethadione. This species difference in anticonvulsant activity between the rat and the mouse has also been found for some other compounds; the data will be reported elsewhere.

In our hands, the procedure of Putnam and Merritt has proved to be a specific test in which the results are more readily reproducible. The method of Toman, Swinyard and Goodman, on the other hand, is a simple and rapid one, permitting the screening of a large number of compounds in a short period. A compound which is active in raising the electric shock threshold of the cat has been found equally potent, or better, in protecting the rat from the extensor component of the convulsion induced by supramaximal shock. The reverse, however, is often not true.

An inspection of data in the table reveals, further, that compounds active against electric shock convulsions have also been shown to be effective drugs in controlling grand mal seizures. The agents weak in anti-metrazol® property are ineffective in control of petit mal epilepsy. Mesantoin,® which is slightly effective in preventing metrazol® convulsions, is believed by some to be capable of reducing petit mal attacks. The high toxicity and the low activity of nirvanol® as compared with diphenylhydantoin or with mesantoin® in cats also confirm the clinical results for this compound.

Phenurone® is said to be of value in the control of mixed grand and petit mal attacks.[6] Our laboratory data indicate that large doses of this drug are required to demonstrate its anticonvulsant property. It is more active against metrazol® shock than against electric shock convulsions. Carbromal is about ten times as effective as phenurone® in preventing metrazol® seizures. The therapeutic efficacy of carbromal in petit mal epilepsy has not been critically tested.

SUMMARY

The anticonvulsant activities of nine antiepileptic drugs were determined with two electric shock procedures: (1) by the increase in electric convulsion threshold in the cat (Putnam and Merritt) and (2) by the

6. Gibbs, F. A.: Personal communication to the authors.

abolition of extensor tonic seizures in rats and in mice (Toman, Swinyard and Goodman). Four types of compounds were selected for study: hydantoins (diphenylhydantoin [dilantin®], mesantoin® and nirvanol®); barbiturates (phenobarbital and mephobarbital [mebaral®]); acetylureas (phenurone® and carbromal N. F.); oxazolidine-2,4-diones (epidon® and trimethadione [tridione®]). The potency values obtained with the two methods agree well in the cat and in the mouse, in the following order: diphenylhydantoin, mesantoin,® nirvanol,® phenobarbital, mephobarbital, phenurone,® carbromal, epidon® and trimethadione. In the rat, on the other hand, the protective doses of mesantoin® and phenobarbital were found to be smaller than those of other drugs.

The anti-metrazol® activities of these compounds were also determined in rats; the order of potency is the reverse of that against electric shock seizures. The laboratory data are compared with the clinical results for these drugs in the treatment of grand and petit mal epilepsy. There appears to be a fair agreement.

PROGNOSIS IN SPONTANEOUS SUBARACHNOID HEMORRHAGE

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IN A FORMER report,[1] Richardson and I discussed in considerable detail the pathologic and clinical aspects of spontaneous subarachnoid hemorrhage due to berry aneurysms based on a study of 118 patients observed in the Toronto General Hospital from 1928 to 1938 inclusive.

In a consideration of the prognosis, it was found that approximately 50 per cent of patients recover from the attack that brings them under observation. There was evidence that unconsciousness at the onset, preexisting hypertension and advanced age made the prognosis a little graver. It was found that when intracerebral bleeding occurs from ruptured aneurysm of the circle of Willis survival is rendered more uncertain. There was no evidence that a history of one or more preceding attacks made the prognosis any worse. Thirty-seven survivors were followed for an average of four years after their discharge from the hospital. It was found that the great majority were well and that only 2 had died. Only 5 patients had had recurrences after discharge, and it was suggested that perhaps the danger of recurrence had been over emphasized.

Since that time a number of publications have appeared in which the prognosis has been discussed (Magee,[2] Dandy,[3] Hamby,[4] Wolf and associates[5]). The figures in two large series of cases studied (Magee,[2]

Read at the Annual Meeting of the Canadian Neurological Society, Montreal, May 21, 1949.

From the Department of Medicine, University of Toronto Faculty of Medicine, and the Medical Service, Toronto General Hospital.

1. Richardson, J. C., and Hyland, H. H.: Intracranial Aneurysms, Medicine **20**:1 (Feb.) 1941.

2. Magee, C. G.: Spontaneous Subarachnoid Haemorrhage, Lancet **2**:497 (Oct.) 1943.

3. Dandy, W. E.: Intracranial Arterial Aneurysms, Ithaca, N. Y., Comstock Publishing Company, Inc., 1944.

4. Hamby, W. B.: Spontaneous Subarachnoid Hemorrhage of Aneurysmal Origin, J. A. M. A. **136**:522 (Feb. 21) 1948.

5. Wolf, G. A., Jr.; Goodell, H., and Wolff, H. G.: Prognosis of Subarachnoid Hemorrhage and Its Relation to Long Term Management, J. A. M. A. **129**:715 (Nov. 16) 1945.

Hamby [4]) conform with ours in showing a mortality just over 50 per cent in the attacks that bring the patients to the hospital. There are, however, reports indicating a considerably lower hospital mortality (Wolf and associates,[5] 33 per cent; Sahs and Keil,[6] 28 per cent). On the other hand, Martland[7] suggested that practically no patient with a ruptured aneurysm ever recovers and that when recovery occurs after spontaneous subarachnoid hemorrhage the condition is most likely due to another cause.

Many of the views expressed in regard to prognosis indicate a feeling of pessimism because of the high initial mortality, the liability of future hemorrhages taking place after the patient's discharge from the hospital and the varying degrees of disability that may remain with patients who survive. For these reasons, surgical treatment is being increasingly advocated, either by arterial ligation (Wechsler and Gross,[8] Jefferson [9] and Murphy [10]) or by craniotomy with direct attack on the aneurysm (Dandy,[3] Wolf and associates,[5] Swain [11]).

Since there are still some aspects of the prognosis in this condition about which opinion is not unanimous and because there is a need for longer follow-up studies of survivors, it has been considered worth while to report our further observations on a large series of patients. In most instances the follow-up studies previously reported have been over comparatively short periods and therefore cannot be accepted as giving an accurate long term picture. My colleagues and I have endeavored to keep in touch with the survivors of our former series over the years and have made similar observations and a follow-up study on the patients admitted to the hospital from 1939 to 1942 inclusive. The entire series now under survey numbers 191, all of whom were admitted to the Toronto General Hospital between 1928 and 1942 inclusive, a period of fifteen years. Of the 191 patients, 100 died within six months of the onset of the attack that brought them to the hospital, and 91 survived. This mortality of 53 per cent is essentially the same as that found in our smaller series.

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6. Sahs, A. L., and Keil, P. G.: Subarachnoid Hemorrhage Caused Ruptured Intracranial Aneurysms, Am. Heart J. **26**:645 (Nov.) 1943.

7. Martland, H. S.: Spontaneous Subarachnoid Hemorrhage and Congenital "Berry" Aneurysms of the Circle of Willis, Am. J. Surg. **43**:10 (Jan.) 1939.

8. Wechsler, I. S., and Gross, S. W.: Cerebral Arteriography in Subarachnoid Hemorrhage, J. A. M. A. **136**:517 (Feb. 21) 1948.

9. Jefferson, G.: Isolated Oculomotor Palsy Caused by Intracranial Aneurysm, Proc. Roy. Soc. Med. **40**:419 (Dec.) 1946-1947.

10. Murphy, J. P.: Surgical Aspects of Subarachnoid Hemorrhage: M. Ann. District of Columbia **18**:119 (March) 1949.

11. Swain, R. D.: The Surgical Treatment of Certain Intracranial Arterial Aneurysms, S. Clin. North America 396 (April) 1948.

AUTOPSY OBSERVATIONS

Autopsies were carried out in 55 cases of spontaneous subarachnoid hemorrhage (table 1), and ruptured aneurysm was observed in 44 cases. In 9 cases no bleeding point was found, but probably aneurysm was the basis of hemorrhage in most, if not all, of these 9 cases. The sac may have been destroyed by the force of the hemorrhage, or, as some of these cases date back many years, the aneurysm may have been missed, owing to inadequate dissection. In 1 of the 2 remaining cases a subtentorial angioma had been diagnosed during life (Richardson and Bagnall [12]); in the other autopsy showed a hemangioma of the right cerebellar hemisphere. The patient was dead on admission to the hospital and had had his first symptoms a few hours before death.

This high incidence of verified aneurysms is of interest in view of a recent suggestion that arterial angioma is a much more frequent cause of spontaneous subarachnoid hemorrhage than is to be suspected during life unless arteriographic examination is carried out (Wechsler and

TABLE 1.—*Autopsy Data on 55 Cases of Spontaneous Subarachnoid Hemorrhage*

Number of Autopsies	Cases of Ruptured Aneurysm	Cases in Which Bleeding Point Was Not Found	Cases of Angioma
55	44	9	2

Gross [8]). Other arterial angiomas that we have observed over the period covered by this study have not been associated with subarachnoid hemorrhage, and from our observations it seems doubtful whether they cause spontaneous subarachnoid hemorrhage with any frequency, except possibly in children. The accumulated evidence from autopsy, arteriographic studies and exposure at operation in other large series of patients (Magee,[2] Dandy,[3] Hamby,[4] Wolf and associates [5] and Jefferson [9]), as well as in our own, indicates a sufficiently high incidence of demonstrable aneurysms as the cause of this clinical syndrome to warrant consideration of the prognosis in unverified cases in terms of aneurysm.

RECURRENT HEMORRHAGES IN HOSPITAL

Of the 100 patients who died, only 26 had more than one episode of hemorrhage during their terminal illness (table 2). The majority of these (70 per cent) had the fatal recurrence in the first two weeks.

12. Richardson, J. C., and Bagnall, A. W.: Recurrent Subarachnoid Haemorrhage Due to an Arterial Angioma of the Cerebellum and Brain-Stem, Canad. M. A. J. **43**:111 (Aug.) 1940.

Analysis of the data on the surviving 91 patients showed only 14 (15 per cent) with clearcut recurrent attacks of hemorrhage during three months after the onset, the hemorrhage taking place in the first two weeks in 50 per cent. All these 40 patients had the recurrent hemorrhage after some recovery from the original attack had been manifest, but in a considerable proportion the recurrence was within a few days, before much attempt at repair could have taken place.

Our findings with regard to recurrent hemorrhage while the patient is in the hospital with an attack of spontaneous subarachnoid hemorrhage do not indicate that it occurs in as high a proportion of cases as was described by Hamby,[4] Magee [2] and Wolf and associates.[5] Hamby reported recurrences (multiple attacks) in almost 50 per cent of his 130 cases, as compared with our 20 per cent. However, our figures support Hamby's statement that patients with multiple episodes of bleeding in the hospital have only about one-half the chance of survival of those with a single episode.

TABLE 2.—*Incidence of Recurrent Hemorrhages During Hospitalization for Spontaneous Subarachnoid Hemorrhage*

	Number	Percentage in First Two Weeks
100 patients with fatal hemorrhage	26	70
91 survivors	14	50
Total	40	

The question has been raised regarding early surgical treatment, such as arterial ligation [8] or craniotomy,[5] in cases of anteriorly situated aneurysms to prevent the recurrence of hemorrhage, with preliminary angiographic studies in all cases in which localization is not possible on clinical grounds. Obviously, surgical measures would have to be carried out very soon after the patient has been admitted to prevent a recurrence in the first two weeks. It will be gratifying if surgical experience on a large scale shows that the mortality from persistent hemorrhage and early recurrence can be reduced. To date, however, it has not been satisfactorily demonstrated that ligation of the common carotid artery, or the more dangerous procedure of ligation of the internal carotid artery, is truly effective in preventing recurrences. In cases of aneurysm of the carotid artery with paralysis of the third nerve and persistent pain, the indications for arterial ligation are much more definite. Satisfactory results were obtained by Jefferson [9] in a series of 23 selected patients treated in this way. It is pertinent to note, however, that his 3 postoperative fatalities from ligature were those of persons in the acute stage of subarachnoid hemorrhage.

Although conservative treatment has been described as "no treatment at all" (Wechsler and Gross [8]), one wonders whether more attention to such measures as complete bed rest for an adequate period, good nursing care, attention to the bowels in order to avoid straining at stool and proper sedation are not very important in lessening the frequency of recurrences within three months of the onset. It has been demonstrated (Richardson and Hyland,[1] Magee [2] and Hamby [4]) that the patient's activities at the onset bear small relation to rupture, which frequently takes place while he is at rest. There is little doubt, however, that after rupture of an aneurysm, activity and straining while healing is incomplete are liable to cause further bleeding. Hamby [4] referred to 5 patients who left the hospital against advice and died of a recurrent hemorrhage within two weeks after their discharge. He referred also to 9 others who died subsequent to discharge (6 within ten months) for whom the duration of rest in bed in the hospital averaged only 28.5 days. Magee [2] found 50 patients (33 per cent) with recurrences in the hospital, 32 of whom died in the first to the seventh week. Magee stated that two thirds of these recurrences took place while the patient was still in bed or was allowed up under the controlled conditions of hospital life. It has been our policy to keep patients at complete rest in bed for a minimum period of eight weeks after bleeding has stopped, and even longer if hypertension exists. It may be that this practice accounts for our lower incidence of recurrences in the hospital and during the months following discharge.

TABLE 3.—*Factors Influencing Prognosis of Spontaneous Subarachnoid Hemorrhage*

	Patients with Fatal Hemorrhage, 100	Survivors, 91
Average age	52 yr.	44 yr.
Preexisting hypertension	20	10
Involvement of brain tissue	59	37

IMMEDIATE PROGNOSIS

The findings in this series of 191 patients confirm our previous observations that unconsciousness at the onset, advanced age and the presence of preexisting hypertension all render the prognosis worse (table 3). The average age of the patients with fatal hemorrhage was approximately eight years greater than the age of those who survived. Between the ages of 60 and 80 there were 48 patients, of whom 33 (69 per cent) had fatal hemorrhages. It was found also that hypertension was commoner among the patients with fatal hemorrhage. The total number of patients with known preexisting hypertension was 30, of

whom 20 (66 per cent) had fatal hemorrhages. Signs of involvement of brain tissue, other than cranial nerves, by hemorrhage was found in approximately 50 per cent of the patients. Sixty per cent of the patients with fatal hemorrhages had such signs, including hemiparesis, hemiplegia, quadriplegia, aphasia, hemianopsia and gross mental confusion, whereas only about 40 per cent of the survivors had such signs. This proportion is essentially the same as that which was found previously and indicates that the prognosis is a little worse in cases with involvement of the brain by the hemorrhage.

Dandy [3] postulated that the immediate result of each rupture depends to a considerable extent on whether or not tissues are in apposition to the artery at the point of rupture. He suggested that if the hemorrhage passes directly into the subarachnoid space the rupture will usually cause death, whereas if it passes into cerebral substance the adjacent tissues may stop the hemorrhage and prevent immediate death. Although this suggestion has a certain validity, I doubt whether it applies in general, and it fails to take into account the serious effects of destruction of cerebral tissue and interference with cerebral circulation that take place with intracerebral extravasation of blood from a ruptured aneurysm.

In our former paper, we referred to several verified cases we had encountered in which the main bleeding from the aneurysm was intracerebral and the associated subarachnoid bleeding was relatively slight. We speculated on the possibility that sudden hemiplegia occurring in young healthy persons without clinical signs of subarachnoid hemorrhage may be due to ruptured aneurysm embedded in cerebral tissue. Verification had not been obtained at that time, and, so far as I know, no such case has yet been described. A few years ago a patient came under observation in whom the hemorrhage appeared to be entirely intracerebral and who died of a recurrent intracerebral hemorrhage, without subarachnoid bleeding.

CASE 1.—P. A., aged 51, had had an amputation of the right leg below the knee but had otherwise been well until Nov. 2, 1945. While driving his car, he suddenly experienced pain in the left frontotemporal region and behind the left eye, accompanied with drowsiness, weakness in the right arm and leg and difficulty in speaking. He attempted to drive home but crashed into another car. He remained at home at rest during the next two weeks. The pain in the head quickly subsided, and at no time did he have any stiffness of the neck. There was rapid improvement in the weakness of the limbs on the right side, but the speech remained affected. On November 18 he complained of visual difficulty in the left eye, and he was referred to the neurosurgical service at the Toronto General Hospital as having a possible brain tumor.

When seen in consultation, he was mentally alert and cooperative. The general physical examination revealed nothing significant. The blood pressure was 120 systolic and 80 diastolic. There was moderate bilateral papilledema with a few small hemorrhages close to the disks. The visual fields were full. He had a moderate

degree of motor aphasia, as shown in spontaneous speech and in naming objects. Visual and auditory comprehension was good. There were no motor, sensory or reflex abnormalities of the limbs.

Because of the sudden onset and the improvement that had occurred, it was evident that he had sustained a vascular accident. It was considered that this was a hemorrhage from a congenital varix in the white matter of the left frontal lobe or from a ruptured aneurysm on the left middle cerebral artery buried deep in the sylvian fissure with bleeding entirely into the cerebral substance. Hemorrhage

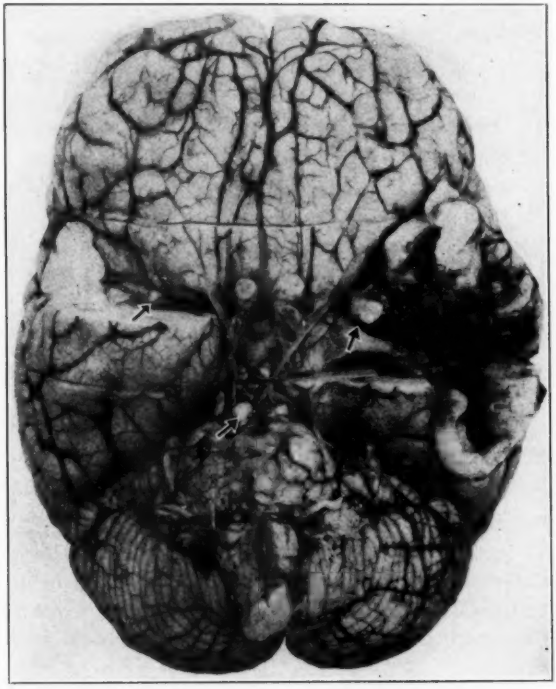

Fig. 1 (case 1).—Brain with the pole of the left temporal lobe removed to show the area of hemorrhage and the calcified aneurysm on the middle cerebral artery, which had ruptured entirely intracerebrally. Two smaller, unruptured aneurysms are present at the bifurcation of the basilar and on the right middle cerebral artery, respectively (arrows).

into a tumor in the left frontal lobe was thought to be a much less likely possibility.

The patient's condition remained stationary. A roentgenogram of the skull showed two very small deposits of calcium in the region of the left sylvian fissure. These were interpreted as suggestive of a tumor, and a ventriculogram, made on November 26, showed displacement of the ventricular system to the right. A bone flap was turned down, and a hemorrhagic cyst was evacuated from the anterior part of the left temporal lobe. The bleeding point was not found. During

the next two weeks the patient showed some improvement in the aphasia and papilledema; but on December 8 there was a recurrence of the pain in the head and he lapsed into coma, dying on December 9.

Autopsy revealed no evidence of old or recent subarachnoid hemorrhage over the cerebral hemispheres or in the spinal canal. A hemorrhagic cavity, containing both old and recent blood, was observed in the left temporal lobe. A large aneurysmal sac with some calcium in the wall was present on the left middle cerebral artery in the stem of the lateral fissure (fig. 1). Its apex was buried in

Fig. 2 (case 1).—Two hemorrhages in the substance of the left frontal lobe. The medial hemorrhage is older and evidently occurred initially, being continuous with the hemorrhage in the temporal lobe. The recent terminal hemorrhage lies laterally.

the tissue of the left frontal and temporal lobes and showed a large rupture of the wall. Two massive hemorrhages were seen in the subcortical white matter of the orbital surface of the left lobe (fig. 2). The larger, and older, of these hemorrhages was continuous with the hemorrhage in the temporal lobe and evidently had occurred on November 2. It lay medial to the recent, terminal hemorrhage. Two small unruptured saccular aneurysms were observed, respectively, on the bifurcation of the basilar artery and on the right middle cerebral artery at the stem of the lateral fissure.

This case illustrates how an aneurysm on a vessel of the circle of Willis embedded in cerebral tissue can bleed entirely into the brain after rupture, causing no subarachnoid hemorrhage. The way in which the initial hemorrhage remained localized and stopped before it had caused any serious generalized interference with cerebral function may have been due to the support provided by the cerebral tissue at the point of rupture, as suggested by Dandy. However, the additional insult to the brain from the second intracerebral hemorrhage, five weeks later, caused rapid unconsciousness and death, which might not have occurred had there been the means of escape for some of the blood into the subarachnoid space.

MULTIPLE ATTACKS

Of the whole group of 191 patients, 28 (15 per cent) are known to have had one or more attacks of hemorrhage other than the one that brought the patient under observation, the interval between attacks being greater than three months (table 4). The fact that only 3 of the 100 patients with fatal hemorrhage had a history of previous attacks makes

TABLE 4.—*Incidence of Multiple Attacks of Hemorrhage in a Series of 191 Patients with Spontaneous Subarachnoid Hemorrhage*

Total number	28 (15%)
Number with fatal hemorrhage in hospital	3
Number who died of another attack (average period, 6.1 years)	14
Survivors (average period, 11 years)	11

it seem possible that these figures do not represent the total number of patients having multiple attacks. A considerable proportion of the patients with fatal attacks were in no condition to give a proper history, and the incidence of previous attack might have been greater had an accurate history been obtainable. It must be significant that of the 17 patients with multiple attacks who died, 11 had a history of preexisting hypertension, whereas none of the 11 survivors had hypertension.

Nineteen patients had only one attack other than that which brought them under observation. Four patients each had three attacks, and 4 others each had four attacks. One patient had five attacks, which took place over a period of eight years, the last attack being fatal. The average time from the first attack until death for the 17 patients who died was six years, whereas the average time from the first attack for the survivors was eleven years.

These figures, although admittedly low because of lack of complete information in some of the fatal cases, do not indicate that the danger of recurrent attacks in patients who have had subarachnoid hemorrhage is as great as might be inferred. It would seem that the presence of

hypertension in patients who have had a ruptured intracranial aneurysm renders them more likely to have a subsequent fatal attack. A possibility that must be considered in any case in which a second attack of subarachnoid hemorrhage develops is that the rupture in the second attack may have occurred in a different aneurysm than that responsible for the first. One such verified case occurred in the present series.

Case 2.—E. S., a woman aged 44, was admitted to the hospital on Sept. 24, 1937. She had begun to have a severe occipital headache about one month previously. The headache improved with a few days' rest in bed, but one week after

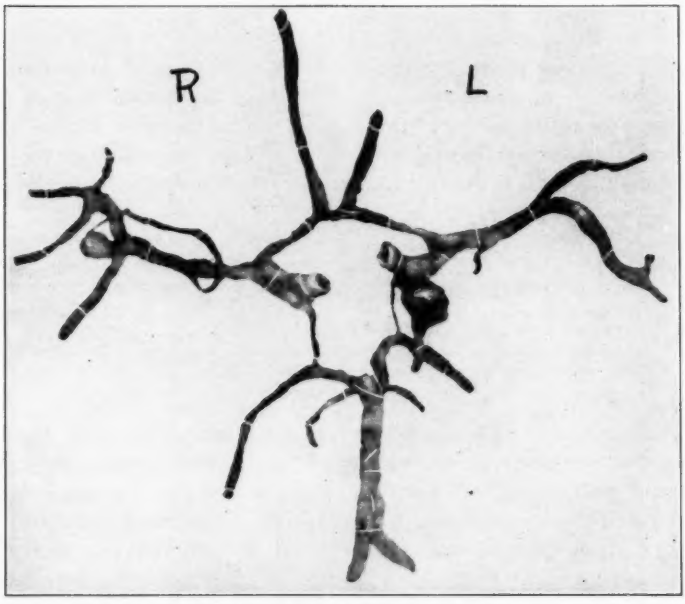

Fig. 3 (case 2).—Dissection of the basal cerebral arteries, showing the two aneurysms. The aneurysm on the right middle cerebral artery had ruptured in 1937. The aneurysm on the left internal carotid artery is seen lying above the third nerve, which was incorporated in the aneurysmal sac. The rupture of the latter aneurysm caused death in 1940.

the onset she collapsed with sudden paralysis of the left side. She remained at home in bed, and the weakness in the limbs improved; but a few days before admission the headache recurred and became very severe.

On admission she was restless and irrational with well marked signs of meningeal irritation. The blood pressure was 225 systolic and 110 diastolic. The heart was enlarged. The fundi showed narrowing of the arteries and several small hemorrhages. There was severe flaccid hemiplegia on the left side. The cerebrospinal fluid had a pressure of 225 mm. and was xanthochromic.

During the next four weeks there was little improvement, but subsequently her mental state improved and there was some recovery of power in the left leg. The blood pressure remained elevated. She was discharged on Jan. 24, 1938, able to walk and with some power in the left arm. The diagnosis was subarachnoid hemorrhage due to ruptured aneurysm in right middle cerebral artery and hypertensive cardiovascular disease.

The patient was readmitted on April 25, 1940. She had carried on her duties as a housewife since her previous admission, and without much discomfort except for the inability to use the left upper limb. On the day prior to her admission, while walking, she had a sudden onset of agonizing pain in the occipital region, and after a few hours she became comatose.

On examination she was unconscious, with signs of meningeal irritation. In addition to the residual signs of hemiplegia on the left side, there was complete paralysis of the left third nerve. The blood pressure was 220 systolic and 120 diastolic. The cerebrospinal fluid was grossly bloody and xanthochromic. The patient regained consciousness during the next few days, and examination on May 2 showed that, in addition to the complete paralysis of the left third nerve, there was some limitation of upward and lateral movement of the right eye. The patient's condition improved during the next few weeks, although the ocular condition remained unchanged. Quite suddenly, on July 9, she became unconscious and death occurred in ten minutes.

Autopsy showed extensive subarachnoid hemorrhage. An aneurysmal sac at the second bifurcation of the right middle cerebral artery had ruptured and eroded the cortex of the posterior end of the right insula, extending to involve the posterior limb of the internal capsule, as evidenced by signs of old hemorrhage and gliosis. This hemorrhage had given rise to the permanent hemiplegia that developed in 1937 (fig. 3). The left oculomotor nerve was partially demyelinated and greatly thinned out. It constituted part of the wall of an aneurysm on the left internal carotid artery, which had ruptured on its posterior aspect. The involvement of this nerve, resulting from the rupture of the aneurysm, accounted for the complete paralysis of the left third nerve associated with the attack which proved fatal in 1940.

The complication illustrated in this case, in which a second spontaneous subarachnoid hemorrhage resulted from the rupture of a different aneurysm than that which was responsible for the first attack, is probably uncommon. However, the possibility of such an occurrence must always be kept in mind, since aneurysms are multiple in about 25 per cent of cases in which they occur. Obviously, any surgical treatment carried out at the time of the patient's first hemorrhage would not have benefited her, and arterial ligation on the right side might have hastened the rupture of the aneurysm on the left side.

ULTIMATE PROGNOSIS

In pursuance of the plan which was in effect when we completed our former study in 1939, an attempt has been made to contact all surviving patients every two or three years. Many of the patients have come to the hospital to be examined, but in some cases we have had to

rely on information by letter from the patient or relatives or on a communication from the family physician. Vital statistics have also been consulted. Since the hospital admissions in this series went back as far as 1928, it has been impossible to trace a number of the patients; but I am able to report later developments for 67 of the 91 patients who recovered and left the hospital. The duration of the follow-up periods from the time of the first attack of hemorrhage varied from twenty-one months to twenty-four years, and the results as known at present are shown in table 5.

Seven patients died of causes other than recurrence of the hemorrhage, and in several instances associated diseases, such as diabetes and

TABLE 5.—*Duration of Follow-Up Period in 67 Patients with Spontaneous Subarachnoid Hemorrhage*

		Average Observation Period	
Number alive when last contacted	46	10.4 yr.	Average 9.4 yr.
Number who died of recurrence subsequent to discharge	14	6.1 yr.	
Number who died of other cause, subsequent to discharge	7	4.0 yr.	

TABLE 6.—*Data on 46 Patients Who Survived Subarachnoid Hemorrhage*

	Number	
No disability	29	63%
Able to work		
Mild disability	10	22%
Moderate disability	4	9%
Unable to work		
Severe disability	3	6%

cardiovascular disease, led to the fatal termination. For 2 cases the available information was not adequate to determine the cause of death, and it is possible that death may have been due to a recurrent hemorrhage. Likewise, for 4 of the 14 patients whose death was attributed to a recurrence of hemorrhage, the description of the terminal illness left some doubt as to its exact nature, but the cases have been included as instances of recurrence on the basis of probability. There is thus a mortality from recurrence of hemorrhage of about 20 per cent of the 67 patients who were followed up. Of the 60 patients who were alive when last contacted or who had died of a recurrence of subarachnoid hemorrhage, the average follow-up time since the initial attack which brought them to the hospital was 9.4 years.

SYMPTOMS DEVELOPING IN SURVIVING PATIENTS WHO WERE FOLLOWED UP

The 46 surviving patients for whom follow-up records are available have been under observation for varying periods—in some instances for many years, the average being over ten years (table 6). Included with the 29 patients described as having no complaints when last examined are several who had various symptoms, such as headaches, fatigue, mild hemiparesis and even some aphasia, for periods of a year or two after leaving the hospital. These symptoms gradually improved, so that the patients were able to carry on their usual lives without disability. In this connection, it is possible that the much higher incidence of residual symptoms of a disabling character mentioned in some reports may have been due to the comparatively short period that elapsed between the attack and the follow-up report. Magee [2] stated that the prospect of a really good recovery was poor. He cited the series of 22 surviving patients whom he reexamined, finding 18 with persistent complaints of varying severity. However, for only 1 patient was the period between the attack of hemorrhage and the follow-up report longer than two years and for 13 patients it was a year or less. It is possible that if these patients had been followed longer, further improvement would have been noted, in some instances at least.

The 10 patients who had persistent mild disabilities but who were able to work complained of such symptoms as headaches, mild residual weakness in the limbs of one side, mental dulling and residual pareses of the third nerve, but in no case were the symptoms sufficient to cause the patient much distress or to interfere with gainful occupation. Of the 4 patients who had moderate disabilities but were able to work, 3 had hemiplegia, in 1 of whom it was associated with aphasia and convulsions. The convulsions of the latter were well controlled with medication, and the patient is carrying on at factory work in spite of some motor speech defect and a useless right arm. The case of the fourth patient is of interest as illustrating how local effects of an aneurysm can cause the development of new symptoms after recovery from the results of rupture. Large aneurysms giving rise to symptoms by pressure occasionally occur, but these do not usually rupture. In this case the first evidence of the lesion was a severe attack of subarachnoid hemorrhage, from which the patient recovered, but with the lapse of years there have developed new symptoms of a progressive nature, indicating local involvement by the aneurysm itself.

CASE 3.—M. O., a woman aged 45, first came under observation on April 23, 1938, with symptoms of severe subarachnoid hemorrhage of one week's duration. There were no localizing signs, and her general physical condition was excellent. She improved with complete rest in bed, but on May 5 and 21 and June 10,

respectively, she had severe recurrences of bleeding. With the third recurrence there were noted slight temporary ptosis of the right lid and dilatation of the right pupil.

During the next three months the patient showed progressive improvement except for exacerbation of headache late in July, which lasted a few days. All symptoms and signs subsided, and she was allowed up on September 15 and discharged home for further convalescence on October 4. The diagnosis was ruptured aneurysm of the right internal carotid artery.

She was readmitted to the hospital on Nov. 26, 1946, for investigation of headaches on the right side, severest behind the right eye, which had been present intermittently for six months. It was stated that she had been well since her previous admission, having given birth to three children and being able to perform all her strenuous duties as a housewife without difficulty. However, in 1940 she began to have momentary lapses of consciousness, which would come on suddenly with a sensation as though everything were fading into the distance and were

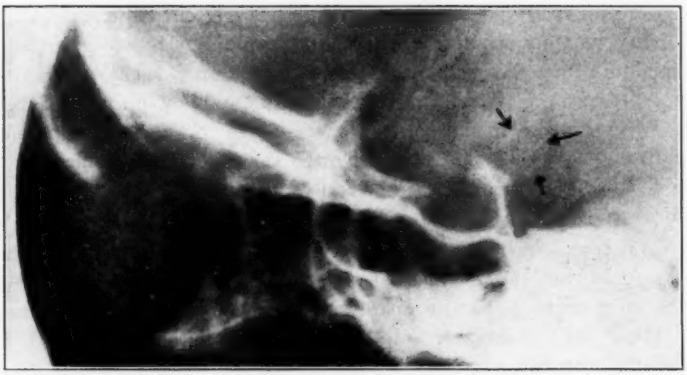

Fig. 4 (case 3).—Lateral view of the skull, showing a spherical calcified lesion suggesting a saccular aneurysm. This lay to the right of, and immediately behind, the sella turcica and probably arose from the internal carotid artery above the level of the anterior clinoid processes.

unreal. She would stop what she was doing, and be unable to speak, and her face would become fixed for a second or two. About once a week she would have three or four of these attacks in a day. In 1945 she had an attack with loss of consciousness in which she sustained a severe scald from a kettle of hot water she was carrying. After this she was placed under anticonvulsant medication, which lessened the frequency of her attacks.

Examination revealed nothing significant. The patient had stated that at the height of her severe attacks of right-sided headaches she had noted that her right eyelid drooped, and this statement was confirmed by observation in the hospital. The cerebrospinal fluid was entirely normal. A roentgenogram of the skull showed a deposit of calcium to the right of, and immediately behind, the sella turcica, in the form of a sphere almost 1 cm. in diameter (fig. 4). The shape and position suggested a saccular aneurysm, probably arising from the internal carotid artery

or from one of its branches. An electroencephalogram showed a continuous discharge of high voltage, slow waves arising from a focus deep in the right temporal lobe.

In the hospital the patient continued to have frequent attacks of petit mal and occasional severe headaches in the right frontal region. It was decided, with the

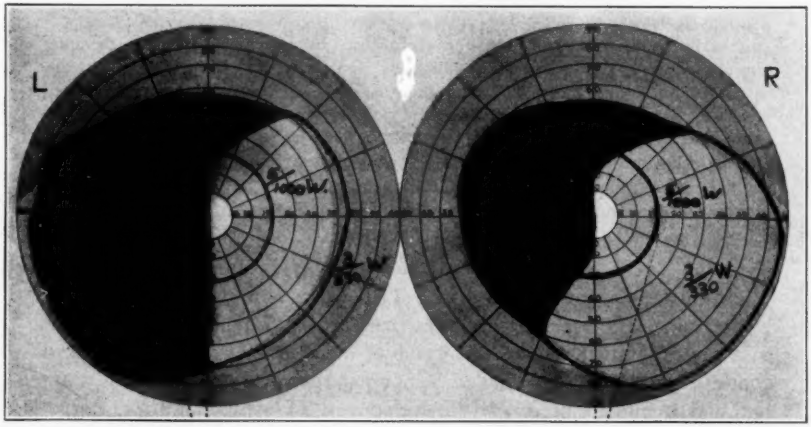

Fig. 5 (case 3).—Visual fields, taken in April 1949. The incongruity of the left homonymous hemianopsia and involvement of central vision suggest the optic tract as the site of the lesion.

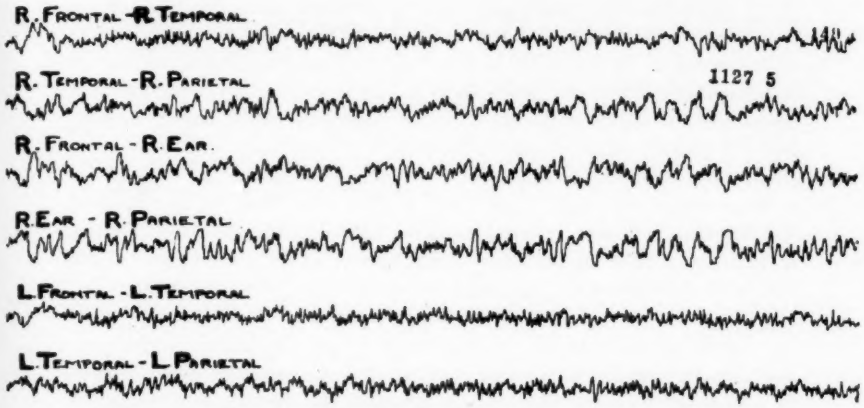

Fig. 6 (case 3).—Electroencephalogram. The tracing from the left temporal region appears normal. A continuous discharge of medium and high voltage, slow waves arises from the deep temporal region of the right hemisphere.

evidence of an aneurysm in the region of the right internal carotid artery and the severe pain, that the right common carotid, or possibly the internal carotid, artery should be ligated. Accordingly, increasing digital pressure on the common carotid artery in the neck was carried out daily, but it was never possible to

produce pressure longer than three or four minutes without the patient's experiencing rather marked paresthesias in the left arm and leg. It was noted that the digital pressure carried out while the headache was in progress did not lessen the severity of the pain. It was decided that arterial ligation was not advisable, and the patient was discharged under a regimen of anticonvulsant therapy with doses sufficient to render her petit mal attacks infrequent. Before she left the hospital, her severe headaches had almost entirely subsided.

She has been followed as an outpatient since her discharge from the hospital and has remained able to carry on with her usual activities. Petit mal attacks are infrequent as long as she takes anticonvulsants. The headaches have not been frequent, although they are occasionally very severe and are accompanied with ptosis of the right eyelid. In November 1948 she complained of difficulty in reading and mistiness of objects when looking to the left. Her visual fields showed a slightly incongruous left upper quadrantanopsia, which had become an almost complete hemianopsia when last tested, in April 1949 (fig. 5). A second electroencephalogram (fig. 6) and a roentgenogram of the skull showed essentially the same condition as on the previous examinations.

In this case a patient who had had a severe spontaneous subarachnoid hemorrhage with three recurrences over a period of three months, due to a ruptured aneurysm in the region of the internal carotid artery, had continued with no recurrence of hemorrhage for a period of eleven years but had exhibited progressive development of symptoms from direct involvement of neighboring structures by the presumably enlarging aneurysm. Although the roentgenologic appearance suggested that the aneurysm was in the region of the right internal carotid artery, the third nerve has never been permanently affected, although it has shown a temporary disturbance of function repeatedly, associated with attacks of hemicrania. It is probable that the attacks of petit mal are due to involvement of the right hemisphere by the aneurysm, and possibly their focus is in the region of the thalamus, as suggested by the recent observations of Jasper and Fortuyn Droogleever.[13] The recent development of the incongruous left hemianopsia involving central vision is probably due to pressure on the right optic tract by the aneurysm. Unfortunately, the results of digital compression of the carotid artery preclude ligation in this case. One, of course, is apprehensive about the future, but the patient is by no means incapacitated by her symptoms at present and leads an active life as a housewife and mother of small children.

The 3 patients who are unable to work and who suffer from severe disability include a man who has had hypertensive cardiovascular disease, as well as aphasia and right homonymous hemianopsia, since his attack of subarachnoid hemorrhage. Another patient has had persistent aphasia and right homonymous hemianopsia. The third patient had right hemiplegia and aphasia with her original attack of spontaneous subarachnoid

13. Jasper, H. H., and Fortuyn Droogleever, J.: Experimental Studies on the Functional Anatomy of Petit Mal Epilepsy, A. Research Nerv. & Ment. Dis., Proc. **26**:272, 1946.

hemorrhage, in 1932. She recovered from the aphasia and was able to carry on fairly well for many years. In the past two or three years she has shown progression in the form of amblyopia, and it is probable that the aneurysm is exerting local pressure effects, as in the case just cited.

The results in this group of 46 surviving patients observed over a long period indicate that the majority of patients who survive are able to carry on with no handicap and that relatively few are seriously disabled. The incidence of fatal recurrences (20 per cent) in an average follow-up period of ten years is fairly high, but not alarming. The most serious aspect of the disease is the high initial mortality, and it is to be hoped that surgical measures, which are being employed with increasing frequency, will prove effective in lowering this mortality rate. However, at the time of an attack it is often not possible to tell whether the patient will survive or whether he will have a fatal recurrence either in the hospital or at some time later. Therefore caution has to be used in subjecting patients to procedures involving risk. The observations on this group of patients suggest that those who survive the initial hemorrhage with medical treatment only have a good chance of carrying on for years without disabling symptoms and without recurrence of the hemorrhage.

SUMMARY

Observations on 191 patients with spontaneous subarachnoid hemorrhage occurring between 1928 and 1942 are reported, with particular attention to prognosis.

In 44 of 55 autopsies, ruptured aneurysm was demonstrated as the cause, and in only 2 instances was another lesion found. It is believed that the frequency with which aneurysm is shown to be the cause of spontaneous subarachnoid hemorrhage justifies consideration of the prognosis in terms of aneurysm in unverified cases.

The findings confirm previous observations that the mortality rate approximates 50 per cent and that the prognosis is made a little worse with advancing years, the presence of preexisting hypertension and extension of the hemorrhage into brain tissue.

The question of recurrent bleeding in the hospital is discussed, and the desirability of a period of rest in bed, with good nursing care, of not less than two months is emphasized.

Three cases are reported. The first case illustrates the occurrence of intracerebral hemorrhage from an aneurysm without subarachnoid bleeding. In the second case hemorrhages, occurring three years apart, arose from different aneurysms. The third case illustrates long survival after severe hemorrhage and later development of local pressure effects by an enlarging aneurysm.

A follow-up study of 67 patients is reported. Although only 15 per cent of the total series had more than one clearcut attack at intervals greater than three months, 14 (20 per cent) of the 67 survivors are known to have died subsequent to discharge of another attack in an average period of 6.1 years.

Forty-six patients have been followed for varying periods and were alive when last contacted. These have been under observation for an average of more than ten years. Twenty-nine are free from symptoms, and only 3 are so severely incapacitated as to be unable to work.

It is concluded that patients who survive the initial hemorrhage have an 80 per cent chance of carrying on for a considerable number of years without recurrence and a good prospect of being free from any persistent residual disability.

Dr. J. G. Richardson assisted in this study; Prof. E. A. Linell aided in the pathologic observations, and Dr. E. H. Botterell permitted the publication of case 1.

604 Medical Arts Building (5).

HISTOLOGIC STUDY OF THE BRAINS OF MONKEYS AFTER EXPERIMENTAL ELECTRIC SHOCK

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SINCE the introduction of electric shock in the treatment of certain mental disorders, numerous investigators have attempted to determine whether this form of therapy produces histologic changes in the central nervous system. It has not been shown conclusively that changes do occur. The problem was restudied by subjecting monkeys to treatment similar to that employed in human electric convulsion therapy. After shocks of various duration, the animals were killed and the central nervous system was prepared for histologic examination by improved and rigidly controlled technical procedures that precluded postmortem cellular deterioration.

MATERIALS AND METHODS

Five male monkeys (Macaca mulatta), weighing 8 to 10 pounds (3.6 to 4.5 Kg.), were treated; an additional monkey served as a control. All were kept together in a large cage and were fed an adequate diet of fresh fruits and vegetables and the standard prepared laboratory chow. Throughout the experiment, the animals appeared healthy, showed only slight fluctuations in weight and manifested no alterations in their behavior.

The shocks were administered three times a week with a Rahm 60 cycle apparatus equipped with a recording surge current meter that had been previously standardized and that gave a permanent record of the current flow during the exposure. The animal was placed in a chair beneath a transparent table with the head projecting through an adjustable aperture. A bar at the level of the hips held the animal loosely in the chair. The head was held manually for temporary application of the electrodes during the passage of the current. The electrodes measured 7 mm. in diameter and were applied to the frontoparietal region after preliminary shaving and application of electrode paste.

Treatment of the individual monkeys differed in respect to the number of shocks (thirteen to nineteen) and to the duration of the current flow (0.1 to 0.4

This study was aided by a grant from the Faculty Research Fund.

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Presented in part, by title, at the Seventy-Fourth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 13-15, 1949.

second). Some further slight variation between the shocks was due to differences in the resistance. The potential was constant at 90 volts for all exposures. The resistance, kept as low as possible, varied from 290 to 900 ohms, while the current varied from 90 to 310 milliamperes. During each individual shock these factors were relatively stable. The table summarizes the data.

Three animals (B, C and E) were killed twenty-four hours, and 2 animals (A and D) forty-eight hours, after the last convulsion. This was accomplished with a perfusion-fixation technic.[1] While the animal was under light pentobarbital sodium anesthesia, the ascending portion of the thoracic aorta was cannulated, and the entire vascular system was perfused with a 2.4 per cent solution of acacia in isotonic solution of sodium chloride, the blood and fluid leaving through an incision in the right atrium. Immediately after the perfusate became grossly free of blood, and while the heart was still beating, solution of formaldehyde U. S. P. in 10 per cent concentration in the acacia–sodium chloride solution was perfused through the same cannula. The hydrostatic pressure was maintained at 85 cm. of water. By introducing the large acacia molecule into the perfusing and fixing solutions, edema was prevented and a satisfactory balance between the hydrostatic and the osmotic pressure maintained. The whole procedure took about eight minutes; fixation

Summary of Courses of Treatment

Animal	Number of Treatments	Duration of Current, Sec.	Average Current, Ma.	Range of Current, Ma.	Average Resistance, Ohms
A	16	0.1*	189	160-240	487
B	13	0.2	187	145-240	493
C	16	0.3	196	110-290	488
D	13	0.4†	230	145-290	405
E	19	0.4	211	90-310	454

* On the tenth exposure, duration was 0.4 second.[5]
† On the tenth exposure, duration was 0.3 second.[5]

began in four minutes, while the heart was still beating. In contrast to the conventional methods of fixation by immersion, this technic insured almost immediate preservation of the deeper, as well as the more superficial, parts of the central nervous system.

The brain and spinal cord were removed and placed in formaldehyde–sodium chloride solution for further hardening. One half of each brain was saved for future cytochemical investigations. Blocks of representative regions from the other half were embedded in pyroxylin of low viscosity. The regions selected for study were the frontal, temporal and occipital lobes; the anterior and posterior central gyri, the basal ganglia, the brain stem and the cervical portion of the spinal cord. These included parts of the brain lying between the electrodes.

Sections were cut serially at 30 microns and were stained with a buffered thionine method for nerve cells,[2] a method for myelin[3] and a silver impregnation

1. Koenig, H.; Groat, R. A., and Windle, W. F.: A Physiological Approach to Perfusion-Fixation of Tissues with Formalin, Stain Technol. **20**:13-22 (Jan.) 1945.

2. Windle, W. F.; Rhines, R., and Rankin, J.: A Nissl Method Using Buffered Solutions of Thionin, Stain Technol. **18**:77-86 (April) 1943.

3. Weil, A.: A Rapid Method for Staining of Myelin Sheaths, Arch. Neurol. & Psychiat. **20**:392-393 (Aug.) 1928.

technic for axons.[4] With a p_H of 4.5, the thionine method differentiates the glial nuclei, as well as their cytoplasm (lightly), and is excellent for nerve cells. Experimental and control sections were stained together in the same dishes as a further means of controlling the technic and facilitating comparison.

RESULTS

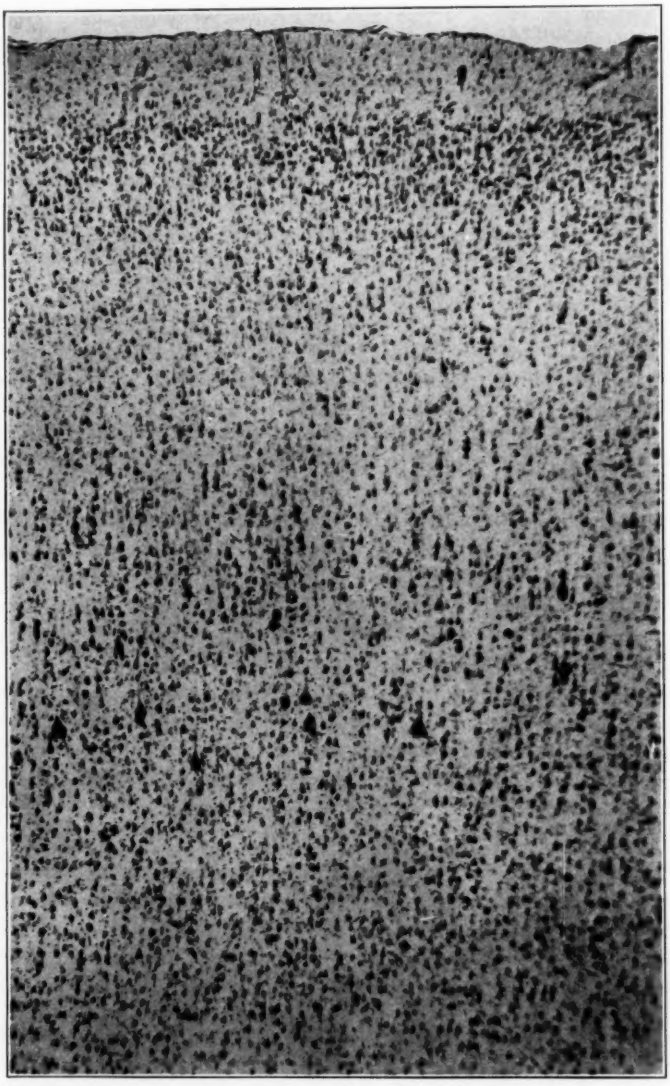
Each treatment led to a grand mal seizure. With the passage of the current the animal was thrown into a generalized tonic fit, followed several seconds later by clonic twitchings associated with apnea. After a variable period, lasting less than forty-five seconds, a flaccid phase, marked by deep breathing and absence of deep reflexes, ensued. Ten to thirty second later the animal became hyperexcitable and usually, though not always, exhibited increased deep reflexes, purposeless movements, anxiety and sometimes screaming. The duration of the clonic phase was generally proportional to the duration of the shock, lasting longest in animals receiving the longest shocks. Thus, animal A had a momentary reaction, while animals D and E (table) had seizures lasting up to forty-five seconds; in animals B and C the duration of the reaction was proportionately between these extremes.[5] The duration of the convulsion was also proportional to the amount of current.

Involuntary urination and defecation were occasionally observed during the clonic phase. During this phase the pupils were unresponsive to light. Both mydriasis and miosis were seen during the early part of the convulsion, but the pupils always became completely dilated toward the end of the seizure and returned to normal during the flaccid stage. One animal (E) consistently exhibited piloerection after the subsidence of the excitement stage; another (C) showed this phenomenon occasionally. Animal E manifested ataxia for about five minutes after the seizure; animals C and D were ataxic infrequently, but only after the severer shocks. Nystagmus was rarely present; the eyes in the few instances were more commonly deviated to the left. Salivation occurred occasionally in animal C.

Histologic comparison of the central nervous system of the experimental and the control animals revealed no structural differences. The neurons and the glial elements were of normal appearance throughout the series. There was no evidence of punctate or perivascular hemorrhages, either old or recent. Even the region between the electrodes,

4. Holmes, W.: A New Method for the Impregnation of Nerve Axons in Mounted Paraffin Sections, J. Path. & Bact. **54**:132-136 (Jan.) 1942.

5. This relation was borne out in the tenth treatment of animals A and D: The former was exposed for 0.4 second and had a reaction similar to that seen ordinarily in animals D and E; animal D was exposed for 0.3 second and exhibited a decrease in the clonic phase time as compared with that usually observed in animal C.



Photomicrograph of area 4 of the cerebral cortex of monkey D; × 70.

demonstrated by others [6] to carry the current, was without aberration. The cerebral cortex appeared to have a normal pattern after electric shock (figure), and the individual cells were exactly similar to those of the control. The hippocampus, basal ganglia and nuclei of the brain stem and the spinal cord were without cytopathologic change. Neuronophagia, chromatolysis, sclerotic neurons, hyperplastic glia, granular cells with pigment and foam cells, mentioned by other investigators, were not seen in our preparations. Accumulation of hemosiderin or red blood corpuscles could not be demonstrated in or around the perivascular spaces. The numbers of astrocytes and oligodendrocytes were not increased. Sections stained for myelin sheaths revealed no areas of demyelination. The axons in the silver preparation were well preserved and gave no indication of degenerative changes. In short, the sections both of the experimental and of the control specimens were of uniformly normal appearance and were indistinguishable from each other.

COMMENT

The physiologic reaction of monkeys during and after electric shock treatments is well known and, being similar to that which has been described by others clinically [7] and experimentally,[8] need not be of immediate concern. Consideration can be confined to the histologic observations. Some change may be assumed to be induced by the passage of the electric current in certain human patients; clinical improvement after electric shock suggests this. However, the healthy monkeys appeared to be unaffected in the intervals between bouts of shock. If any alterations took place in the finer structure of their brains, they were not revealed by the technics used. Cytochemical studies will be undertaken later. All that can be concluded now is that no intrinsic morphologic alteration was demonstrated by rigidly controlled histologic technics.

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6. (*a*) Weeks, A. W., and Alexander L.: The Distribution of Electric Current in the Animal Body: An Experimental Investigation of 60 Cycle Alternating Current, J. Indust. Hyg. & Toxicol. **21**:517-525 (Dec.) 1939. (*b*) Alexander, L., and Weeks, A. W.: Electric Shock: Importance of the Path, Distribution and Density of the Current in Determining Symptoms and Pathology, Am. J. Path. **17**:601-602 (July) 1941. (*c*) Alexander, L., and Löwenbach, H.: Experimental Studies on Electro-Shock Treatment: Intracerebral Vascular Reaction as an Indicator of the Path of the Current and the Threshold of Early Changes Within the Brain Tissue, J. Neuropath. & Exper. Neurol. **3**:139-171 (April) 1944.

7. Kalinowsky, L. B., and Kennedy, F.: Observations in Electric Shock Therapy Applied to Problems of Epilepsy, J. Nerv. & Ment. Dis. **98**:56-67 (July) 1943.

8. Ferraro, A.; Roizin, L., and Helfand, M.: Morphologic Changes in the Brain of Monkeys Following Convulsions Electrically Induced, J. Neuropath. & Exper. Neurol. **5**:285-308 (Oct.) 1946.

Disseminated neuropathologic changes of varying severity following experimental electric shock comparable to human therapy have been reported by a number of other investigators.[9] A few authors, notably Alpers and Hughes [10] and Heilbrunn and Weil,[11] reported that hemorrhages occurred but that there were no neuronal changes except in regions contiguous to the hemorrhages. Several other groups of observers,[12] who also used dose ranges comparable to those in human therapy, failed to note any histologic alterations in the brain that they could attribute to the electric shock.

The occurrence of hemorrhages in the brain after electric shock treatments may be due to vasomotor reactions occasioned by the convulsion and not by the current itself. Heilbrunn's later work [13] suggested this. Misplacement of the electrodes may be partly responsible.[6c] Alexander and Löwenbach [6c] were able to produce histologic changes in cats, but only with currents considerably in excess of those ordinarily used for therapy, and then only in the path of the current, which Alexander and

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9. (*a*) Cerletti, U., and Bini, L.: Le alterazioni istologiche del sistema nervosa nell' electroshock, Riv. sper. di freniat. **64**:311, 1940; cited by Ferraro, Roizin and Helfand.[8] (*b*) Neubuerger, K. T.; Whitehead, R. H.; Rutledge, E. K., and Ebaugh, F. G.: Pathologic Changes in the Brains of Dogs Given Repeated Electric Shocks, Am. J. Med. Sc. **204**:381-387 (Sept.) 1942. (*c*) Lidbeck, W. L.: Pathologic Changes in the Brain After Electric Shock: An Experimental Study on Dogs, J. Neuropath. & Exper. Neurol. **3**:81-86 (Jan.) 1944. (*d*) Spiegel-Adolf, M.; Spiegel, E. A.; Ashkenaz, E. W., and Lee, A. J.: Physico-Chemical Effects of Electrically Induced Convulsions: Cerebrospinal Fluid Studies, ibid. **4**:277-290 (July) 1945. (*e*) Ferraro, Roizin and Helfand.[8] (*f*) Ferraro, A., and Roizin, L.: Cerebral Morphologic Changes in Monkeys Subjected to a Large Number of Electrically Induced Convulsions, Tr. Am. Neurol. A. **73**:166-169, 1948.

10. Alpers, B. J., and Hughes, J.: Changes in the Brain After Electrically Induced Convulsions in Cat, Arch. Neurol. & Psychiat. **47**:385-398 (March) 1942.

11. Heilbrunn, G., and Weil, A.: Pathologic Changes in the Central Nervous System in Experimental Electric Shock, Arch. Neurol. & Psychiat. **47**:918-930 (June) 1942.

12. (*a*) Barrera, S. E.; Lewis, N. D. C.; Pacella, B. L., and Kalinowsky, L.: Brain Changes Associated with Electrically Induced Seizures: A Study in the Macacus Rhesus, Tr. Am. Neurol. A. **68**:31-35, 1942. (*b*) Globus, J. H.; Van Harreveld, A., and Wiersma, C. A. G.: The Influence of Electric Current Application on the Structure of the Brain of Dogs, J. Neuropath. & Exper. Neurol. **2**:263-276 (July) 1943. (*c*) Alexander and Löwenbach.[6c] (*d*) Winkelman, N. W., and Moore, M. T.: Neurohistologic Findings in Experimental Electric Shock Treatment, J. Neuropath. & Exper. Neurol. **3**:199-209 (July) 1944. (*e*) Windle, W. F.; Krieg, W. J. S., and Arieff, A. J.: Failure to Detect Structural Changes in the Brain After Electrical Shock, Quart. Bull., Northwestern Univ. M. School **19**:181-188, 1945.

13. Heilbrunn, G.: Prevention of Hemorrhages in the Brain in Experimental Electric Shock, Arch. Neurol. & Psychiat. **50**:450-455 (Oct.) 1943.

his co-workers [6] had previously demonstrated to be essentially confined to the region between the two electrodes. It was also determined by Alexander and Löwenbach [6c] that 300 milliamperes led to a brief period of vasoconstriction in the path of the current and that it took over 2,000 milliamperes (20 milliamperes per square millimeter) to cause irreversible neuronal changes in the current pathway. Apparently, a vasospasm of brief duration is incapable of bringing about structural changes in the neurons of the brain.

Most of the widespread neuronal alterations, so frequently described,[9] are nonspecific. They are seen even in the brains of control animals, as noted by Neuman, Cohn and Katzenelbogen [14]! Barrera, Lewis, Pacella and Kalinowsky [12a] stated very pointedly that the cytopathologic changes seen in experimental animals would have been thought to have been produced by the electric shock had identical pictures not presented themselves in the control. However, Ferraro and Roizin [9f] more recently declared that a quantitative estimation of changes was possible in their study with monkeys. They observed tigrolysis, pyknotic and shrunken neurons, neuronophagia, ghost cells, granular cells with pigment, rarefaction of neurons and other phenomena, and they interpreted these as the result of the electric shock treatments.

Interestingly, phenomena similar to those reported after electric shock were seen in untreated animals by Koenig and Koenig [15] in studying the development of postmortem artefacts in the brain. By using the perfusion-fixation technic for accurately timing the fixation, they demonstrated that postmortem cellular deterioration begins within thirty minutes after death. Furthermore, it has been shown that the more commonly employed immersion-fixation method produces a gradient of fixation from the surface inward.[16] The perfusion-fixation method, when used under controlled hydrostatic and osmotic conditions and without delay, eliminates the autolytic changes which so often cloud the picture of normal brain structure.

It is important also to control the staining procedures if tissues are to be critically studied for neuronal changes. The buffered thionine technic that was employed here is a progressive staining method with a definite advantage over methods that require overstaining and decolorization, for it allowed more exact comparisons to be made between the control

14. Neumann, M. A.; Cohn, R., and Katzenelbogen, S.: Experimental "Shock Therapies" in Cats with Insulin and Metrazol: Histopathologic Study, Am. J. Psychiat. **98**:668-672 (March) 1942.

15. Koenig, R.: Post Mortem Changes Within the Central Nervous System, Anat. Rec. **103**:61 (March) 1949. Koenig, H., and Koenig, R.: Personal communication to the authors.

16. Mayer, E.: The Unspecific Properties of Thyroid Colloid, Anat. Rec. **103**:71 (March) 1949.

and the experimental material. It is noteworthy that with this same method the glial elements were also stained adequately, so that use of special procedures for these cells was unnecessary. This method of staining subsequent to perfusion and fixation has been used previously to demonstrate the subtle changes following concussion,[17] inanition [18] and asphyxiation.[19] In all these studies certain more extensive autolytic changes were recognized with the immersion-fixation technic. These disadvantages were eliminated by the present technic. Failure to recognize postmortem artefacts may explain much of the cytopathologic alteration reported by other investigators who have attributed their observations to the electric shock.

SUMMARY

Five monkeys were given courses of electric shock treatments comparable to those used in human convulsion therapy. An additional monkey served as a control. After the last treatments of the experimental animals, all were killed and the brains fixed by an improved technic of intravascular perfusion and fixation to prevent the development of postmortem artefacts in the brain and spinal cord.

Histologic study of sections of the central nervous system stained by precisely controlled neurologic methods revealed no difference between the experimental and the control animals. There were no neuronal changes, glial proliferation, areas of demyelination or evidence of old or recent hemorrhages in either series. No structural alteration was demonstrated after experimental electric shock.

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17. Windle, W. F.; Groat, R. A., and Fox, C. A.: Experimental Structural Alterations in Brain During and After Concussion, Surg., Gynec. & Obst. **79**:561-572 (Dec.) 1944.

18. Liu, J. C.: Nerve Cell Changes Resulting from Starvation, Anat. Rec. **103**:68 (March) 1949.

19. Jensen, A. V.; Becker, R. F., and Windle, W. F.: Changes in Brain Structure and Memory After Intermittent Exposure to Simulated Altitude of 30,000 Feet, Arch. Neurol. & Psychiat. **60**:221-239 (Sept.) 1948.

EFFECT OF PATHOLOGIC ANXIETY ON INDUCTIVE REASONING

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MARKED disorders of reasoning may be observed in patients who are emotionally very disturbed. Thinking disorders and confusional states are well recognized but have been studied only slightly in cases of manic excitements and depressions. Little mention is made in the literature of marked disorders of reasoning which may occur transiently in anxiety neuroses and in psychoneurotic and psychopathic reactions under the influence of intense emotion. Patients of high intelligence are unable to reason well during these episodes, which may be brief or prolonged.

The present study attempts to clarify the type of thinking disorder which occurs, the psychopathologic setting and the role of specific emotional factors. In the experiments to be described, patients in whom there seemed to be a disturbance of reasoning were studied. Some of these patients were retested after the disorder of reasoning had disappeared. These disorders of reasoning occurred in different psychopathologic settings and in severe anxiety, and other strong emotions seemed to be present. It therefore became necessary to determine the role of various emotions in these disorders.

PROCEDURE

A series of tests has been developed for the study of inductive reasoning (Welch and Long [1]). A long series of problems of increasing complexity is presented to the patient. The most difficult problems in this series can be solved by 13 and 14 year old children. The tests include three-dimensional problems, pictorial problems, linguistic problems and a classification test.

Three-Dimensional Problems.—The apparatus contains six blocks which are plugged into holes connected with light bulbs. A figure is pasted on the surface of each block. The patient is requested to determine the causal factor which lights a bulb in two rows of pictures but not in a third row. This factor can be recognized by the presence of the same class of picture in the two rows with the light and by

From the New York Hospital and the Department of Psychiatry, Cornell University Medical College.

1. Welch, L., and Long, L.: Psychopathological Defects in Inductive Reasoning, J. Psychol. **21**:201-226, 1946.

the absence of this type of picture in the row without a light. Among the concepts used in the test for three-dimensional problems are fruits, vegetables, animals and vehicles. The test makes use of concepts of increasing abstractness.

Classification Test.—After the three-dimensional problems have been finished, the patient is given all the eighteen blocks with the request to arrange them into six groups of three each which belong together. The result is a grouping of fruits,

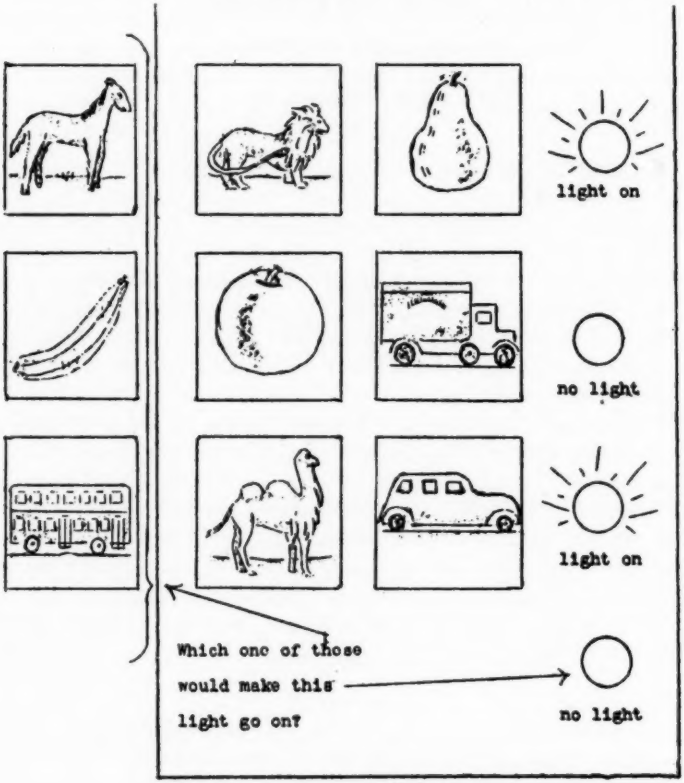

Fig. 1.—The three-dimensional test.

vegetables, people, animals, boats and cars. The next request is to form three groups of six blocks, resulting in groupings of foods, mammals and vehicles.

Pictorial Problems.—Essentially the same type of problem is presented by offering cards to the subject. While in the three-dimensional test concrete material was given, the pictorial test brings out the subject's ability to generalize the principles he has been applying.

Linguistic Problems.—Problems are presented to the patient in printed form which correspond to the problems of the three-dimensional and of the pictorial

tests. In the instructions preceding these linguistic problems, the patient is requested to discover the kind of food that makes a certain person sick. In the following problem, for instance, three classes of foods are used; in the succeeding problems increasingly larger and more involved groups of foods are presented, demanding higher types of abstractions.

Perch	Pear	sick
Tabasco	Peach	well
Ketchup	Flounder	sick
Gravy, plum, carp		

Time Factor.—The experience with children and with a group of medical students indicates that the problems presented in the written linguistic problems can be solved in a range of from twenty to ninety minutes. It can be stated that, statistically, a time of more than ninety minutes should be considered abnormal.

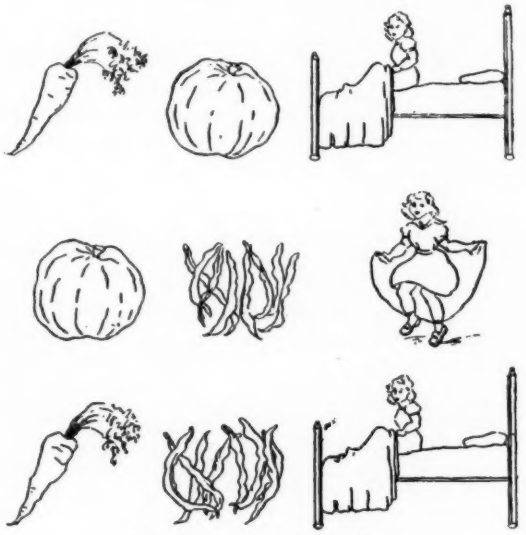

Fig. 2.—The pictorial problem.

The criteria for the three-dimensional and for the pictorial problems were three consecutive successful trials, accompanied with an adequate explanation. A score of failure is made if no adequate explanation is given in a span of 10 trials. The linguistic test consisted of 100 problems divided into 10 different types. An average of 8 correct answers out of a possible 10 was taken as the criterion for each of these 10 groups of problems. The three-dimensional classification and pictorial tests were given on one day; the written tests, on the same day or, if necessary, during the following two days.

CLINICAL MATERIAL

The experiment was administered to patients who were of superior intelligence, judging from their education and life achievement. To over one-half the patients the Wechsler-Bellevue Intelligence Scale was administered, and the results confirmed

this impression. All these patients suffered from a disturbance of reasoning which was obvious clinically by their vague use of concepts, by a tendency to rambling and frequently by inadequate definitions in the psychiatric examination. In some patients this thinking disorder persisted for several days or weeks. In others it became obvious only when anxiety-producing problems were discussed. The first observations of the latter type were made in patients with psychopathic personalities who were treated for psychoneurotic disorders and in psychoneurotic patients. Later, observations on these transient disorders were also made in some depressed patients. Another group was comprised of elated patients. In addition, a number of patients who experienced severe anxiety without obvious disorders of reasoning were investigated. As a considerable number of the patients with anxiety and thinking difficulties had schizophrenic disorders, schizophrenic patients with and without obvious anxiety were studied. These schizophrenic patients did not show the type of transient disorders of reasoning described but demonstrated varying degrees of the many types of thinking disorders found in schizophrenic patients. In no case were the thinking disorders of a degree which did not permit good use of attention, concentration and full cooperation. In the present study, young patients with intellectual defects and marked anxiety were excluded, as well as patients with cerebral arteriosclerotic and other cortical disorders. There was included a small group of alcoholic patients in whom the possible influence of anxiety on reasoning in the presence of toxic factors was investigated.

OBSERVATIONS

Types of Failures.—In the total series of 187 patients studied, 92 failures occurred with some of the written linguistic problems, 26 with the three-dimensional problems and 6 with the pictorial problems. Nineteen patients had failures in classification. The time was abnormally prolonged for 54 patients. No failures occurred without the presence of anxiety. Retests were administered after an interval of from six weeks to several months to 22 patients whose anxiety had subsided. All these patients had shown numerous failures in the first series of experiments and had no failures in the repeated series. One patient had no failures in the first study, when he was free of anxiety but showed failures in a retest in the presence of anxiety.

The highest number of failures (36 patients) occurred in the most difficult linguistic problems, i. e., problems 9 and 10. With more pronounced marked disorders of reasoning, these failures might include problem 8 and preceding problems. The number of failures was indicative of the degree of the disturbance in reasoning, but not of the intensity of the anxiety present or the type of the psychopathologic setting. Failures at isolated points in this test, a written one, were observed in 21 patients. These failures occurred in patients with mild disorders of reasoning, with anxiety-produced inadequacy and fear of not performing well. Failures at the beginning of the written test (6 patients) denoted anxiety to the test situation in patients who in life had shown an attitude of inadequacy to test situations but who did well after getting started. It is not possible to make the statement that performance of

the repeated test several months later without failure was due to the fact that pathologic anxiety had subsided. Familiarity with the test and knowledge of the previous final success may have prevented this type of failure in a repeat test, even if performed in the setting of mild or moderate pathologic anxiety. Five patients with clinically marked disorders of comprehension and grasp had failures in the three-dimensional problems. Two patients were deeply depressed; 2 were bewildered ("confused") and schizophrenic; 1 was alcoholic with depression. These failures occurred with good performance in the other tests. In 21 patients with pronounced thinking disorders, failures occurred in the three-dimensional problems as well as in the written, and occasionally the pictorial, tests. The disorders in these 21 patients included schizophrenic and depressed conditions. Failures in the three-dimensional problems did not seem to relate to the degree of anxiety.

Failures with the pictorial problems were observed in 6 patients. These failures were always concurrent with failures in the written tests in patients with clinically pronounced thinking difficulties. This group included 5 schizophrenic patients and a depressed alcoholic patient. Anxiety was severe.

Three patients were found to fail in classification alone—the first, a psychopathic young woman with strong anxiety; the second, a 42 year old woman with elation, marked anxiety and underlying depression; the third, a youth of 16 with paranoid schizophrenia and moderate anxiety. Failures in classification and in the written and the three-dimensional tests were made by 16 patients, including 7 with schizophrenia, 1 with paranoia, 3 with psychopathic personalities, 3 with depressions, 1 with elation and 1 with depression complicating alcoholism. The disorders of classification always occurred in the setting of a severe psychopathologic disorder of the type mentioned and with moderate to strong anxiety.

Abnormally prolonged time, i. e., longer than ninety minutes for the total experiment, was noted for 20 patients, who performed well otherwise. This group included 9 patients with depressions, 2 of whom showed strong paranoid projections and 1 compulsions; 4 with paranoid schizophrenia and 1, slightly ambivalent, with a catatonia; 1 with psychopathic personality; 1 with compulsion neurosis and 2 with anxiety neuroses; 1 with a paranoic disorder and 1 with a hypomanic state. Prolonged time, together with failures in other tests, was observed for 34 patients, including 15 with depressions, 8 with schizophrenic illnesses, 2 with paranoid reactions, 3 with psychoneuroses, 4 with psychopathic personalities, 1 with mild manic excitement and 1 with depression accompanying alcoholism. An analysis of the records of these patients revealed that cautious and suspicious attitudes, indecisiveness and compulsive characteristics were frequently present. There was no indication that retardation of the depressive type was definitely a factor.

Types of Psychopathologic Reaction and Failure.—A study of the relation of failures in these tests to the psychopathologic setting revealed some significant facts, in addition to the points previously mentioned. The total group studied comprised 40 patients with psychopathic personalities (with 14 failures), 24 with psychoneurotic disorders (with 7 failures), 54 with depressions (with 35 failures), 12 with hypomanic and mildly manic reactions (with 7 failures), 8 with paranoid reactions (with 3 failures), 45 with schizophrenia (with 26 failures) and 4 with depression associated with alcoholism (with 4 failures). An analysis of the results for these groups is tabulated.

Psychopathic personalities		40
Anxiety present	22	
Failures	14	
Normal results	8	
Patients without anxiety	18	
Normal results	All	
Psychoneurotic disorders		24
Anxiety present	18	
Failures	7	
Normal results	11	
Patients without anxiety	6	
Normal results	All	
Depressions		54
Anxiety present	47	
Failures	35	
Normal results	12	
Patients without anxiety	7	
Normal results	All	
Moderate manic excitements		12
Anxiety present	7	
Failures	All	
Patients without anxiety	5	
Normal results	5	
Paranoid reactions		8
Anxiety present	5	
Failures	3	
Normal results	2	
Patients without anxiety	3	
Normal results	All	
Schizophrenic disorders		45
Anxiety present	26	
Failures	All	
Patients without anxiety	19	
Normal results	All	
Alcoholism with depression		4
Anxiety present	4	
Failures	All	

There emerges the striking fact that in all types of psychopathologic settings failures in the reasoning experiments occurred only in the presence of anxiety. Anxiety as such, however, does not produce failures, as is obvious from our observation that in various psychopathologic disorders normal results may also be obtained in the presence of anxiety.

In psychopathic personalities of various types, transient disorders of thinking were observed under the influence of strong anxiety. The following case serves as an illustration.

CASE 1.—A married woman aged 26 reacted with anxiety and mild depressive features to rejection by her lover. She was an intelligent woman who had grown up as a rejected child in a disharmonious family. She was unable to form a lasting

close attachment to either parents or siblings and showed poor social adjustment, which became pronounced in adolescence. She was anxious and insecure, withdrawing into her life of phantasy and reacting readily with mild suspiciousness. In her premarital and marital sexual life she had usually searched for sexual satisfaction with various men. Her ethical standards were poorly formed. Her life did not change essentially with her marriage at 23. She was unable to focus on goals which might give her permanent satisfaction; she was dissatisfied and moody but vivacious and an excellent conversationalist in a group. During five months of study and treatment she discussed many dynamic factors. Whenever highly anxiety-producing material was reviewed, she became vague, hiding the anxiety at times behind flippancy. In the psychiatric examination she described anxiety and showed poor attention (6 digits forward) and concentration (2 mistakes in serial subtraction), gave inadequate definitions (misery—"a condition that arises whether you are poor or not") and was frequently vague in her statements. The Wechsler-Bellevue Intelligence Scale gave a full scale intelligence quotient of 117 (verbal intelligence quotient, 109; performance intelligence quotient, 124). When the examination was repeated when she was free from anxiety, she showed no pathologic responses.

EXPERIMENT 1 (January 28 to 30).—In relation to psychotherapeutic discussions the patient had been in a state of considerable anxiety for several days.

Three-dimensional test:

Group.....	1	2	3	4
Failures....	7 (out of 10)	2 (out of 6)	1 (out of 4)	9 (out of 20)

Classification test: No failures
Pictorial problems: No failures
Linguistic written problems:

Series.....	1	2	3	4	5	6	7	8	9	10
Errors.....	0	0	1	0	1	0	0	1	2	3[2]
(out of 10)								Time: 105 min.		

EXPERIMENT 2 (March 30-April 1).—The patient felt at ease during a phase of psychotherapy which was not disturbing emotionally.

Three-dimensional test:

Group.....	1	2	3	4
Failures....	0	0	1 (out of 5)	0

Classification test: No failures
Pictorial problems: No failures
Linguistic written problems:

Series.....	1	2	3	4	5	6	7	8	9	10
Errors.....	0	0	0	0	1	2	0	0	0	0
(out of 10)								Time: 80 min.		

These observations are typical of the failures which occurred in the studies on this series of psychopathic personalities. In some of these patients anxiety-produced disorders of reasoning occur so readily that they may be observed by others in daily life, giving the impression that the patient is unintelligent or superficial.

CASE 2.—A woman aged 41, of superior intelligence, had suffered at times since late adolescence from frequent attacks of mild depression and at others from mild elation. These so-called mild elations consisted of ill concealed strong anxiety and sexual excitement. In the depressive episodes, and more so in the elated episodes, she became vague in the use of concepts and often rambled to a degree which made it difficult to follow her trend of thought. Between these periods, from one to several years, the patient was supposedly in good health, a successful hostess, well

2. A score of three or more errors is considered a failure.

able to assume considerable responsibility and to participate in involved financial discussions. Since childhood, which was characterized by rejection on the part of both parents, she had felt insecure, especially in the presence of brilliant or intellectually aggressive people. In arguments with such persons, she experienced marked anxiety and her reasoning became affected. The awareness of this difficulty increased her anxiety. At 39, and again at 41, the patient was advised to undergo planned psychotherapy in the Payne Whitney Clinic because her reacting with thinking difficulties to anxiety-producing therapeutic discussion prevented analytic discussions in planned psychotherapy.

EXPERIMENT 1 (January 17).—The patient felt at ease in the hospital environment, and there was indication of only mild anxiety, revealed in increased pulse rate and mild elation. When asked to participate in the test, she became distractible and overtalkative, with vague thinking. She had considerable difficulty in concentrating on the three-dimensional test. She felt at ease with the written test, not showing the psychopathologic symptoms noted, and performed well.

Three-dimensional test:

Group.....	1	2	3	4
Failures....	0	6	10	1
(out of 10)				

Classification test: There were no failures, but explanations were extremely complex; e. g., instead of stating that her reason for grouping fruits and vegetables together was because they were "food," she said that she put them together because "they are things that people require and they are produced by people."

Pictorial problems: She failed the first 5 trials, then solved the next 3 trials correctly.

Linguistic written problems:

Series.....	1	2	3	4	5	6	7	8	9	10
Errors.....	0	0	1	0	0	2	3	0	1	2
(out of 10)								Time: 105 min.		

EXPERIMENT 2 (June 10).—The patient was at ease during the test, which was administered during a phase of psychotherapy which was not emotionally disturbing.

Three-dimensional test:

Group.....	1	2	3	4
Failures....	0	0	0	0

Classification test: No failures

Pictorial problems: No failures

Linguistic written problems:

Series.....	1	2	3	4	5	6	7	8	9	10
Errors.....	1	0	0	0	0	0	1	0	1	0
(out of 10)								Time: 30 min.		

EXPERIMENT 3 (November 11).—The patient was retested at a time when she was in a state of prolonged anxiety and tension with some mild depression. Her reaction was related to considerable difficulties with her husband. She was aware of difficulty in comprehension, was vague in the use of concepts and rambled.

Three-dimensional test: Not given

Classification test: Not given

Pictorial problems: Not given

Linguistic written problems:

Series.....	1	2	3	4	5	6	7	8	9	10
Errors.....	1	0	0	0	0	2	3	1	0	2
(out of 10)								Time: 50 min.		

In the following case it was possible to administer the first series of experiments in the absence of anxiety, when normal results were obtained. A few weeks later, in a phase of anxiety, many failures occurred.

CASE 3.—A successful business man aged 38 had suffered from mild anxiety for fifteen years. He was aggressive and had to make his success against unscrupulous competition. At 34 he was seen in consultation because of increased anxiety

and mild paranoid projections. At that time vagueness in thinking was noted. At 38, owing to his wife's unfaithfulness and increased business strain, he again became anxious and discouraged and felt rejected by his friends. In the hospital (October 14) he did not present depressive symptoms but was circumstantial and rambling in conversation and blamed himself for leaving his business. Anxiety was poorly described and was indicated by his inadequate attention. He soon felt encouraged during a phase of psychotherapy which was directed at the analysis of his life achievements.

EXPERIMENT 1 (October 18).—The patient felt at ease during a phase of psychotherapy which was not emotionally disturbing.

Three-dimensional test:

Group.....	1	2	3	4
Failures....	0	0	0	1 (out of 10)

Classification test: No failures
Pictorial problems: No failures
Linguistic written problems:

Series.....	1	2	3	4	5	6	7	8	9	10
Errors.....	0	0	0	0	0	3	0	0	1	0
(out of 10)								Time: 50 min.		

EXPERIMENT 2 (January 23).—The patient had been under considerable anxiety during the preceding days, was vague in discussions and circumstantial.

Three-dimensional test:

Group.....	1	2	3	4
Failures....	5 (out of 8)	0	0	0

Classification test: No failures
Pictorial problems: No failures
Linguistic written problems:

Series.....	1	2	3	4	5	6	7	8	9	10
Errors.....	0	0	0	0	0	3	1	0	4	1
(out of 10)								Time: 21 min.		

A paranoid reaction with depression and marked anxiety is presented in the following case.

CASE 4.—A divorced woman aged 44 reacted with paranoid delusions to promotion to a position with increased responsibility, to difficulties with employees and to indecision about remarrying her divorced husband. Within two months her delusions of persecution, with marked guilt feelings and depression, increased. She became very fearful and made a suicidal attempt. During the psychiatric examination, she appeared slightly vague in her statements and was anxious and tense; her attention was impaired (7 digits), and her concentration was inaccurate (serial subtraction, 1 mistake; slow). Her depression became more obvious and anxiety increased. She heard voices accusing her of misdeeds, and she felt insecure in the hospital, making interpretations which confirmed her delusions of persecution.

EXPERIMENT 1 (May 15).—The patient was under considerable anxiety; she felt depressed and hopeless.

Three-dimensional test:

Group.....	1	2	3	4
Failures....	0	1 (out of 4)	0	1 (out of 11)

Classification test: No failures
Pictorial problems: No failures
Linguistic written problems:

Series.....	1	2	3	4	5	6	7	8	9	10
Errors.....	0	0	0	0	0	2	1	3	10	5
(out of 10)								Time: 125 min.		

EXPERIMENT 2 (November 23).—After the patient had shown gradual improvement under psychotherapy, the depression was interrupted by the administration of ten electrically induced convulsions (terminated on November 2). The few days

before the test she felt at ease, free from hallucinations and delusions, but resentful toward being urged to continue psychotherapy in the hospital.

Three-dimensional test:											
Group	1			2			3			4	
Failures	1 (out of 4)			0			0			1 (out of 10)	
Classification test: No failures											
Pictorial problems: No failures											
Linguistic written problems:											
Series	1	2	3	4	5	6	7	8	9	10	
Errors (out of 10)	0	0	0	0	0	0	0	0	0	0	Time: 85 min.

With several patients these tests were administered before and after convulsive therapy. From patients with normal findings before the treatment, normal results were obtained afterward. For patients with failures before treatment, the results after termination were either improved or normal, according to the degree of clinical improvement and decreased anxiety.

Schizophrenic patients failed in the experiment in the presence of anxiety. In the absence of anxiety these patients performed well. Anxiety was obvious from the patient's description and from physiologic findings. In all these patients vagueness of thinking and occasional incoherence accompanied anxiety. Patients both with and without anxiety had well recognizable schizophrenic developments and psychopathologic manifestations of the various clinical types. The case related for presentation is typical of the whole group. As in many of the schizophrenic subjects, her thinking disorder was noticeable during interviews but was difficult to describe.

CASE 5.—An unmarried laboratory technician aged 27, when assigned to unfamiliar work with increased responsibility, became insecure and tense. She was troubled by a love affair. After two months of tension there suddenly developed thought crowding, an overwhelming feeling of guilt, "confusion," delusions of being dead and of being tested by colors. She heard the voice of her lover advising her and became fearful of impending disaster. She became slow, said little and was vague, often incoherent. After four days she was brought to the hospital, where these psychopathologic manifestations persisted for three weeks. Her attention was decreased (6 digits), and concentrations was inadequate (2 errors in serial subtraction). Abstract differentiations were well done, but metonymic distortions [3] occurred occasionally during interviews. On the Wechsler-Bellevue Intelligence Scale she obtained a full scale intelligence quotient of 132 (verbal intelligence quotient, 134; performance intelligence quotient, 124). The patient, an insecure girl of superior intelligence, had had a similar schizophrenic illness at 23 which subsided after six weeks. Another exacerbation had occurred at the age of 24, lasting a year. During the succeeding year she worked well in her field but had an unsatisfactory social life. During the second and third months of treatment, the patient made steady progress, but whenever she was pushed in interviews she became anxious and slow and had difficulty in expressing herself.

3. Cameron, N.: Reasoning, Regression and Communication in Schizophrenics, Psychol. Monogr. **50**:1-34, 1938.

EXPERIMENT 1 (October 12).—The patient was anxious and slow and felt guilty.

Three-dimensional test:

Group.....	1	2	3	4
Failures....	2 (out of 5)	0	1 (out of 4)	0

Classification test: No failures
Pictorial problems: No failures
Linguistic written problems:

Series.....	1	2	3	4	5	6	7	8	9	10
Errors.....	0	0	0	0	0	1	0	0	7	4
(out of 10)								Time: 195 min.		

EXPERIMENT 2 (December 21).—The patient was at ease except when sensitive problems were discussed in interviews. Then she became anxious and slow, had difficulty in expressing herself and was vague. The tests did not disturb her.

Three-dimensional test: Not given
Classification test: No failures
Pictorial problems: No failures
Linguistic written problems:

Series.....	1	2	3	4	5	6	7	8	9	10
Errors.....	0	0	0	0	0	0	0	0	0	0
(out of 10)								Time: 60 min.		

Interesting observations were made on 4 alcoholic patients who had been heavy drinkers, used barbiturates and had become mildly depressed. In the hospital, after they had been free from addiction to alcohol and barbiturates for two to three weeks, these patients still presented such far reaching thinking difficulties that in each case cortical damage or inadequate intellectual endowment was considered. After about four weeks, the thinking difficulties rapidly disappeared. Depression was not marked and quickly subsided within these four weeks.

CASE 6.—A married woman aged 54 had felt restless for a year and took barbiturates daily. For two months she had been drinking heavily. As she had poor control over her emotions and threatened suicide, she was admitted to the Payne Whitney Clinic on February 15. The patient had been dissatisfied in general for many years, sexually frigid and estranged from her husband. She has always been insecure, anxious and dependent on alcohol for social security. For ten years she had been a steady drinker. In the clinic she was tense and suspicious, resentful and anxious. Her speech was circumstantial, rambling and repetitive. Her attention was slightly impaired (7 digits), and she had considerable difficulty in concentration. Her general information was poor, and her definitions were vague and personalized. On March 26 she was able to repeat only 5 digits and showed some improvement in concentration, but her information was still poor and her definitions were inadequate. There was little insight into her difficulties, which she smilingly brushed aside.

EXPERIMENT 1 (March 7).—The patient was tense and anxious. On the Wechsler-Bellevue Intelligence Scale she obtained a full scale intelligence quotient of 114 (verbal intelligence quotient, 110; performance intelligence quotient, 113).

Three-dimensional test:

Group.....	1	2	3	4
Failures....	10 (out of 10)	Not given [4]	Not given [4]	Not given [4]

Classification test: Not given
Pictorial problems: No failures
Linguistic written problems:

Series.....	1	2	3	4	5	6	7	8	9	10
Errors.....	0	0	0	0	2	0	0	5	7	8
(out of 10)								Time: 75 min.		

4. The problems in groups 2, 3 and 4 were not presented because of complete failure on group 1.

EXPERIMENT 2 (April 24).—At the end of March the patient began to improve rapidly, and all her psychopathologic symptoms had disappeared by the middle of April.

Three-dimensional test:										
Group.....	1		2			3			4	
Failures....	0		0			1 (out of 4)			0	
Classification test: No failures										
Pictorial problems: No failures										
Linguistic written problems:										
Series.....	1	2	3	4	5	6	7	8	9	10
Errors.....	0	0	0	0	0	2	1	1	1	2
(out of 10)								Time: 45 min.		

Two other alcoholic patients who are not included in this group had 1 failure in the reasoning experiment in the presence of anxiety two weeks after abrupt withdrawal of alcohol. This observation seems to indicate that a toxic effect can persist for a considerable period after consumption of alcohol has been discontinued. There was no indication that the brains of these patients had been damaged. Mild damage, however, can never be ruled out completely. The point of possible cortical damage is important because it has been established that anxiety can have a far reaching disturbing effect on intellectual functions in persons with beginning and advanced cerebral arteriosclerosis. This fact has been established with regard to memory functions. In patients with cerebral arteriosclerosis who were included in the group reported on in this publication, inductive reasoning was affected to a greater degree in the presence of anxiety than in the absence of this emotion. A similar observation was made on oligophrenic patients.

COMMENT

Experimental studies on inductive reasoning have demonstrated that in the presence of anxiety failures may occur. No failures have been observed in the absence of anxiety. This phenomenon, however, does not occur in every patient who suffers from pathologic anxiety. A considerable number of the patients who had the same psychopathologic condition and who seemed to experience a similar degree of anxiety performed without any failures. There is no indication as to what factors permit anxiety to have this far reaching influence on reasoning in some patients. A careful study of the personalities involved has not furthered our understanding. Psychopathologic considerations also have not been helpful. A large number of these patients seemed to suffer from psychoneuroses and psychopathic personalities, but no definite relation to present psychopathologic and genetic-dynamic factors could be established. A considerable number of the younger patients were physically somewhat immature and showed immature personalities, but not to an extent which could be considered significant.

Electroencephalographic studies were not contributory. Normal and pathologic electroencephalograms were obtained in an equal number of cases. Most of the pathologic electroencephalograms occurred in the

cases of psychopathic personality and corresponded to those which Diethelm and Simons had found for patients of this type. At no time was there an improvement in the electroencephalogram with the subsidence of anxiety and the improvement in reasoning, although some findings were suggestive of such a relation.

The results in the schizophrenic group were surprisingly uniform. They indicate that anxiety can have a far reaching effect on the reasoning of such patients. It will be necessary to review the current concepts of schizophrenic thinking disorders and to determine if possible features which must be attributed not to a specific schizophrenic disorder but to the influence of anxiety.

The disorders in classification remind one of findings of Cameron [5] in his study of schizophrenic thinking which he discusses under the tendency to generalizations. In our observations, the patients were unsuccessful because their generalizations were too broad or too involved.

In this series of experiments, individual differences in reactions to anxiety were revealed, and these must be considered in evaluation of the results. In some patients anxiety led to a hurrying through the tasks, resulting in a further increase of anxiety, and therefore the inability to perform well. In others, anxiety led to initial difficulty in the test. It might be worth while to repeat these experiments with a change in the order in which the tests are given. The prolonged time seemed to be an indirect influence of anxiety. In the largest number of the patients with failures, especially on the linguistic problems, the cause seemed to be the direct influence of anxiety on inductive reasoning.

SUMMARY

A series of experiments for the investigation of inductive reasoning was applied to 187 patients in order to establish the influence of anxiety on reasoning. The experiments had been found to be reliable for children who had passed their fourteenth year (Welch and Long [1]). The correlation between general intelligence and reasoning ability in these tests was very low. The subjects were requested to isolate the stimulus which produced a given effect. In a three-dimensional problem the subject was required to find the causal factor by putting a block in the correct place to light a bulb. The blocks bore pictures of animals, food and vehicles. The causal factor was indicated by the presence of the same picture in the two rows with lights and by the absence of this picture in the row which had no light. The same type of problem was presented with pictures and in a written form. The time was recorded for each experiment.

5. Cameron, N.: Schizophrenic Thinking in a Problem-Solving Situation, J. Ment. Sc. **85**:1012-1035, 1939.

In all cases of failures anxiety was present. The failures were most numerous in the linguistic test (written problems, 92 patients). With 22 patients the experiments were repeated six weeks to four months later, after anxiety had subsided. In all repeated experiments the particular patients performed without failure. Twenty-one patients had failures in the three-dimensional test, while 5 patients had failures with the pictorial material. Three patients were unable to classify the material correctly. For 54 patients the time was prolonged, apparently being influenced by the patient's attitude to the test and not directly by anxiety.

Anxiety affected inductive reasoning adversely in psychoneurotic, psychopathic, depressive, elated, paranoid and schizophrenic patients. It can be stated that anxiety can interfere with inductive reasoning in any of these psychopathologic disorders, but that, on the other hand, the presence of anxiety does not necessarily affect reasoning. No explanation can be offered for this effect of anxiety in some patients. This effect has not been observed with normal anxiety.

The significance of the influence of anxiety on reasoning in schizophrenic patients must be considered in forming any concept of a specific schizophrenic thinking disorder.

Anxiety may prevent psychotherapeutic progress because of its adverse influence on reasoning. This factor may also affect the success of life achievements in some psychoneurotic and psychopathic patients. Clinical signs which may indicate the adverse influence of anxiety on reasoning are vagueness, circumstantiality and rambling, and inadequate definitions. Such clinical manifestations occur in patients readily when anxiety is stirred up and may subside rapidly with the decrease of anxiety. These manifestations may give the impression of inadequate general intelligence.

DISCUSSION

Dr. Russell G. MacRobert, New York: What was the type of electroencephalographic abnormality in the psychotic group?

Dr. Oskar Diethelm, New York: There were slow waves and, in a few cases, the hyperventilation reaction. The findings corresponded to those described for psychopathic personalities.

Dr. Abraham M. Rabiner, Brooklyn: A person with no organic lesion walks into the street and, because there is a strong wind blowing and he is buffeted about, behaves as though he had cerebellar disease. One knows, however, that he has no organic lesion and that he is able to walk. The wind corresponds to the emotions, and the wind of an anxiety state may hamper normal reasoning and other intellectual functions. Is it justifiable then, to say that the patient has abnormal reasoning, and thus imply that he has an intellectual disorder, when his intellect is known to be normal?

Dr. Leo M. Davidoff, New York: In view of the fact that the abnormal results seem to be associated with anxiety, could your test be used in the selection of patients for bilateral lobotomy, especially in treatment of schizophrenia, for

which the results are so uncertain? Could this be a means of making a selection of patients who would be helped by this operation?

Dr. Oskar Diethelm, New York: I do not think one can draw definite conclusions about the usefulness of this test for the selection of patients for bilateral lobotomy.

With regard to Dr. Rabiner's question: One cannot say in such a disorder what is psychopathologic and whether such a condition is present. I would warn against using too readily the expression "the influence of anxiety on thinking," especially when other factors are to be considered. One can say that if anxiety is very severe there may be inability to perceive or grasp a situation in some people, and difficulty of retention or of recall in others. We should be justified in saying that anxiety will affect the reasoning in a relatively small group of persons.

Dr. George H. Hyslop, New York: Has Dr. Diethelm decided which is the cart and which the horse? Some human beings have atypical reactions to standard situations. Are they the persons who may have this faulty synthesis and, because of their maladjustment, acquire an anxiety state, in a way comparable to experimental animals, and to animals whose trainers will not teach them beyond what they are capable of lest anxiety reactions develop? A good human example is furnished by educational missionaries who have been working in the Congo for twenty years; they found that a certain percentage of natives could profit from education up to a certain level, but that if pushed beyond that point they had schizophrenic breakdowns.

Dr. Oskar Diethelm, New York: I cannot answer your question definitely. The electroencephalographic findings, especially when the pathologic changes increase with anxiety, may argue for a neurophysiologic factor. In the other groups, the individual's development in life may form the necessary basis for disorders of reasoning under the influence of intense anxiety.

THE CURRENT PATH IN ELECTRIC CONVULSION SHOCK

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IT IS RATHER commonly supposed that the shock current applied to the head in electric convulsion therapy travels directly from electrode to electrode, in a fairly straight and narrow path, passing undeflected through skin, bone and brain. Alexander and Lowenbach [1] presented data which they interpreted as supporting this point of view, while Smitt and Wegener,[2] using a more direct technic, found evidence which seems to indicate considerable diffusion of the current.

The present experiment resembles that of Smitt and Wegener in employing intracerebral voltage measurements from probes passed through the brain from the occipital protuberance to the supraorbital margin. It differs from theirs in using a live monkey rather than human cadavers, and it includes several additional measurements, which make it possible to estimate the resistivities of the several tissue layers and to study their effects on the distribution of current through the head.

SUBJECTS AND METHODS

Three adult spider monkeys were used in this experiment. Two were used in preliminary work, while developing the technics employed, and 1 was used in the final measurements to supply the data reported here. The experiment was conducted with the monkey under dial® (diallylbarbituric acid) anesthesia.

The shock was supplied by an 800 volt transformer, with a variable amount of series resistance in the secondary circuit and a variable transformer in the primary circuit. It was timed at about 0.25 second by manual operation of a telegraph key. The shock electrodes were copper disks 1 cm. in diameter, placed just above and ahead of the monkey's ears. Electrode jelly was used at all times to insure good contact over the area of the electrodes, but care was taken to confine it to this area.

The intracerebral voltage produced by the shock was picked up by probes which entered the brain through holes drilled in the occipital protuberance and passed toward the supraorbital ridge. There were two sets of probes—one pair,

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From the Yerkes Laboratories of Primate Biology.

1. Alexander, L., and Lowenbach, H.: Experimental Studies on Electroshock Treatment: I. The Intracerebral Vascular Reaction As an Indicator of the Path of the Current and the Threshold of Early Changes within the Brain Tissue, J. Neuropath. & Exper. Neurol. **3**:139-171, 1944.

2. Smitt, J. W., and Wegener, C. F.: On Electric Convulsive Therapy, with Particular Regard to a Parietal Application of Electrodes, Controlled by Intracerebral Voltage Measurements, Acta psychiat. et neurol. **19**:529-549, 1944.

spaced 15 mm. apart, passed through the medial parts of the brain, and another pair, spaced 45 mm. apart, passed just under the lateral surfaces. They were constructed of copper wire, 0.7 mm. in diameter, covered by 1.5 mm. glass tubing, except for 4 mm. at the tip. The ends of the probes were round and smooth, to minimize hemorrhage.

The probes were supported and guided by a frame attached rigidly to the monkey's head by ear plugs and a medial skull screw. This frame also carried a millimeter scale, to facilitate adjusting and measuring the penetration of the probes into the brain.

The voltages picked up by the probes were measured on an oscilloscope with a long persistence screen, by means of comparison with a standard voltage source.

PROCEDURES AND RESULTS

Shock Applied to the Intact Head.—The first measurements were made with a shock current of 58 milliamperes. This was probably about half the convulsion threshold value. The anesthetized monkey jerked rather strongly at each application of this current, but not so strongly as to damage or disarrange the probes or shock electrodes. The potential appearing across the shock electrodes was 54 volts, and the resistance of the intact head was therefore 930 ohms.

The probes were passed forward through the brain, 5 mm. at a time, until they stopped at the anterior wall of the skull. The voltages across them were recorded at each setting.

The distribution of intracerebral probe voltages obtained is shown in figure 1. The data are presented in terms of potential gradients, in volts per centimeter (measured voltage divided by distance between probes), so that if the brain substance is assumed to have uniform resistivity the heights of the curves may be considered proportional to current density. The curves are seen to be quite flat, the peaks being only about 30 per cent higher than the minima. The abrupt rise at the occipital end is an artefact, which will be discussed later. Note that the maximum value of absolute potential difference is only about 1 volt, and that this is for the lateral probes, which included almost the whole width of the brain between them.

The subcutaneous voltage, immediately below the shock electrodes, was picked up by means of pyroxylin-coated needles with bared tips. This value was 26 volts—approximately half the applied voltage.

Shock Applied to the Exposed Skull.—The shock electrodes were temporarily removed, and skin flaps 4 cm. across were turned back at each electrode position. (A 58 milliampere shock was passed through one of these flaps, and the potential appearing across it was found to be 9.5 volts, indicating a resistance of 160 ohms. Since the skin was 1.3 mm. thick, the resistance gradient was about 120 ohms per milli-

meter, with the 1 cm. diameter electrodes used.) Both skin flaps were removed from the head, along with all other soft tissue overlying the skull at this point.

The exposed areas of skull were cleaned and dried, and the shock electrodes were replaced (electrode jelly being used carefully). They were now delivering the shock to points on the skull directly beneath their former positions on the skin.

The shocking current was readjusted to produce the same peak voltage at the lateral probes as had been produced by 58 milliamperes

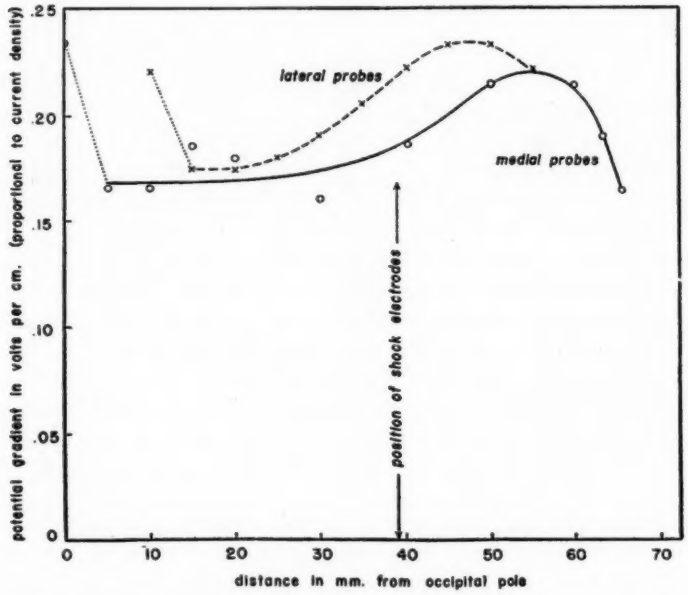

Fig. 1.—Horizontal distribution of current through a monkey's head, as indicated by the voltage gradients picked up by two pairs of probes. A 58 milliampere shock was applied to the intact scalp.

applied to the intact skin. It was found that a current of only 11.6 milliamperes was now sufficient; the difference of 46.4 milliamperes was presumably due to elimination of shunt losses through the extracranial tissue.

The shock electrode potential was 100 volts at the new shock level. This represents a resistance of 8,600 ohms—approximately nine times the resistance of the intact head. Elimination of the extracranial shunt circuit presumably accounts for the change.

Shock Applied Directly to the Brain.—Disks of skull 2 cm. in diameter were next removed at the position of the shock electrodes, which were then once more replaced. They now rested on the dura, directly below their original position on the skin. The shock current was again readjusted to produce the original peak voltage at the lateral probes. The shock level was now 7.0 milliamperes at 2.1 volts, representing a resistance of 300 ohms—only 3.5 per cent of the resistance with intact skull. Since only a very thin layer of tissue was removed between this and the previous resistance measurement, one must con-

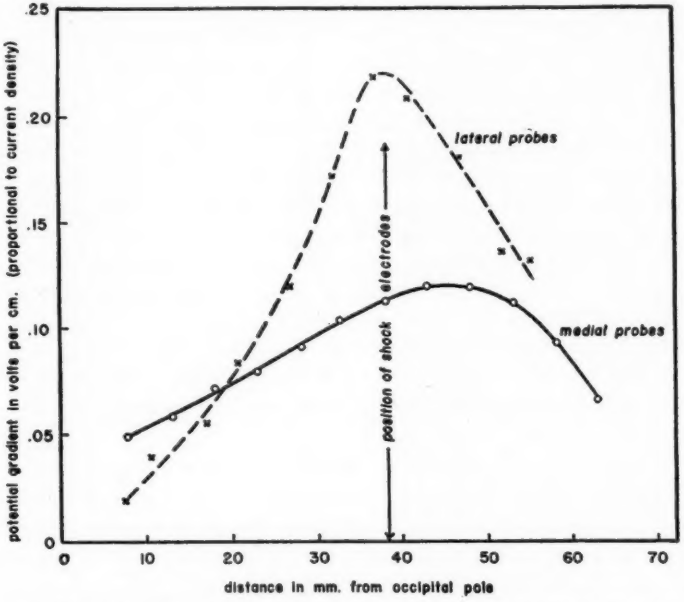

Fig. 2.—Horizontal distribution of current through a monkey's head, with the same setup as that for figure 1, but with a 7 milliampere shock applied directly to the exposed brain.

clude that this layer, the skull, has a very high resistivity, as compared with skin or brain tissue.

The second series of voltage readings at the probes was then taken under these conditions. The distributions obtained are plotted in figure 2. The curves are considerably steeper than those in figure 1; the lateral probes, in particular, indicate a high concentration of current under the electrodes, at the surface of the brain.

Direct Measurement of Skull Resistance.—A large piece of skull was removed from the top of the head, cleaned and dried, and shocks

of 7 and 23 milliamperes were passed through it. The potentials across the shock electrodes were 80 and 200 volts, respectively, for these two current levels, representing resistances of 11,500 and 8,630 ohms. The skull was 2 mm. thick, indicating a resistance gradient of about 5,000 ohms per millimeter, with 1 cm. diameter electrodes. This is about forty times the value found for skin, confirming my previous conclusion as to the very high resistivity of the skull.

This result disagrees quite directly with the conclusion of Weeks and Alexander [3] that various types of tissue are equally good conductors. Their data were restricted to longitudinal conduction in the long bones of the limbs, however, whereas the present study is concerned with the transverse conductivity of the flat, laminated bone of the skull. The amount of vascularization, and its direction relative to that of the current, may account for the difference.

Autopsy.—The monkey was perfused, and the head was hardened in dilute solution of formaldehyde U. S. P. Dissection revealed that the probes had gone essentially where intended. The medial pair had passed through the center of the brain and come to rest against the orbital surface of the skull, about 6 mm. from the frontal pole. The lateral pair had passed directly beneath the shock electrodes, about 5 mm. from the surface of the brain, and had struck the skull at the juncture of the orbital and the lateral surface. The brain was 55 mm. wide, 43 mm. high and 72 mm. long. The shock electrodes had been applied over the superior temporal convolution, about one third of the way back from its anterior end and 41 mm. anterior to the occipital pole of the brain.

COMMENT

The distribution of intracerebral voltages which we obtained for the intact head (fig. 1) is quite similar to that obtained by Smitt and Wegener with parietofrontal electrodes. The curve is rather flat, indicating wide diffusion of the current, with no suggestion of the narrow, sharply bounded path referred to by Alexander and Lowenbach. Failure to find such a discrete route could have been predicted on theoretic grounds: Even if the head does conduct current like a uniform, structureless gel, as Alexander and Lowenbach proposed, the physics of the problem is less simple than they assumed. Electricity does not merely "follow the path of least resistance," as the popular saying has it; rather, it divides among all available paths, the amount following each path being inversely proportional to its resistance. Thus, in the proposed structureless gel, a path twice as long as the most

3. Weeks, A., and Alexander, L.: The Distribution of Electric Current in the Animal Body: An Experimental Investigation of Sixty Cycle Alternating Current, J. Indust. Hyg. & Toxicol. **21**:517-525, 1939.

direct one would carry half as much current. With the usual electrode placement, the current density in the posterior part of the brain might be fully 50 per cent of that at a point midway along the direct path.

If the brain itself is assumed to be electrically equivalent to a uniform, structureless gel (a more probable assumption than that of Alexander and Lowenbach regarding the whole head), then the distribution of figure 2 indicates how the current would be conducted in such a medium. Figure 3 *A*, derived from the data of figure 2, shows the approximate current paths through the brain.

Since the distribution obtained for the intact head is much flatter than that for the brain alone, one must look beyond the normal diffusion of current in a uniform conductor for the explanation. The answer may be found in the high resistivity of the skull. For any given path through the skin, skull and brain, the electrical resistance is predominantly that of the skull: For this reason, alternative current routes (e. g., paths *B* and *C* in figure 3 *B*) pass through considerably greater amounts of skin than does the direct route (path *A*), but since they pass through the same amount of bone, their total resistance will be only slightly greater and they will carry almost as much current. (A sort of "refraction" occurs at the skin-bone and bone-brain boundaries, so that the path segments through the bone tend to remain perpendicular to the surface of the skull, and thus to maintain a constant and minimum resistance.)

Since the flow of current into the brain is largely determined by resistance of the skull, it might be expected that any area of the skull of unusually low resistance would be accompanied with an unusually high current density in the underlying part of the brain. A striking example of this effect is seen in the points at the extreme occipital ends of the curves in figure 1. These points represent measurements made with the probes just entering the brain, and their unusual height is believed due to current from the extracranial tissue flowing into the brain through the holes which had been drilled in the skull to admit the probes. Regions of thin skull would be expected to have a similar effect, accounting perhaps for the fact that the points of maximum current density in figure 1 are somewhat anterior to the position of the shock electrodes.

It will be noticed in figure 2 that the maximum current density at the medial probes is only about one-half that at the lateral probes. This is due to the spreading of the current as it gets farther from the electrodes. Very little of such an effect can be seen in figure 1. Since the extracranial tissue is a good conductor, relative to the underlying skull, it apparently acts as a pair of very large virtual electrodes, each

covering most of one side of the head. That part of the current which penetrates the skull seems to pass across the brain quite directly, from one of these large virtual electrodes to the other, without much spreading.

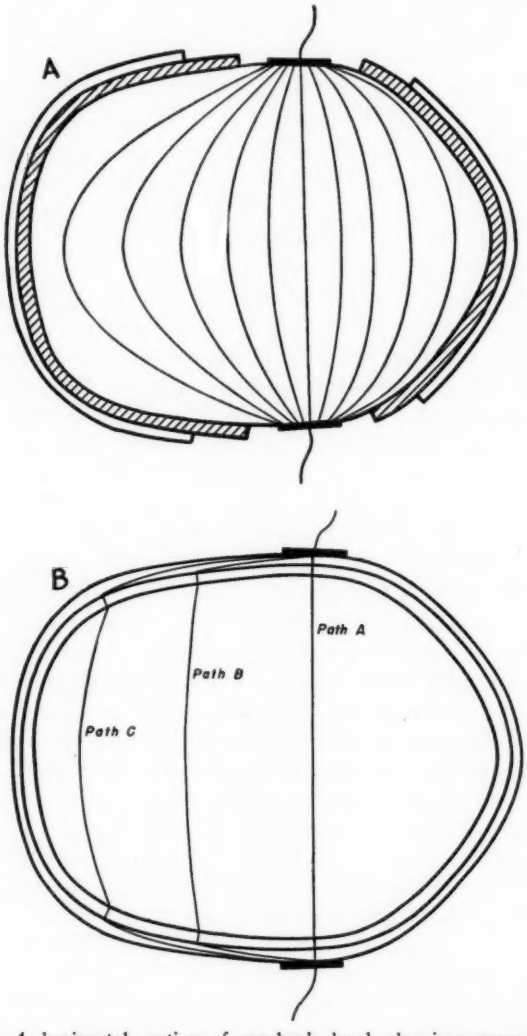

Fig. 3.—*A*, horizontal section of monkey's head, showing approximately the paths followed by the current when shock is applied directly to the exposed brains (derived from data in figure 2). Current density is inversely proportional to spacing of lines. *B*, horizontal section of monkey's head. Although the three current paths shown differ considerably in total length, they have nearly equal total resistances, since they all pass through the same amount of bone.

In addition to making discrete stimulation of specific regions of the brain impossible, the high resistivity of the skull is very important in relation to the division of electrical energy between the brain and the other parts of the head. When the shock was applied to the skin of the intact head, it was necessary to use 3 watts (58 milliamperes at 54 volts) to produce a potential gradient of 0.22 volts per centimeter near the surface of the brain, just under the shock electrodes. When the shock was applied directly to the brain, this same potential gradient was produced with a shock of only 0.015 watt (7 milliamperes at 2.1 volts). The difference was due to the electrical inefficiency of the former procedure: Two hundred times as much energy was needed because most of it was wasted in overcoming skull resistance and by being shunted around the brain in the extracranial tissues.

Two features of this experiment indicate the need of some caution in generalizing to convulsive shock as used clinically: The spider monkey's head is constructed somewhat differently than that of man, and the currents used were weaker than would be needed to produce convulsions. It is believed that both these points are minor ones, however; use of full convulsive doses in human subjects would give results differing in detail, but the essential facts would certainly be confirmed. The spider monkey is more appropriate for this study than most subhuman primates, since its head is more similar to the human head. The skull is thin, and there is little overlying muscle.

SUMMARY

Electrical measurements on an anesthetized monkey during electric convulsion shock have shown certain facts:

1. The skull has a very high electrical resistance.

2. The current flow through the brain is very diffuse. Discrete stimulation of selected cortical areas is not possible when current is applied to the intact scalp.

3. Most of the applied electrical energy is wasted in shunt current losses through the extracranial tissue and in series voltage losses in the skull. Only a small fraction of the applied power is dissipated within the brain.

Dr. Josephine S. Blum assisted me in this study, particularly in connection with the surgical procedures.

Yerkes Laboratories of Primate Biology, Inc.

ELECTRIC SHOCK THERAPY OF ACUTE PSYCHOSIS ASSOCIATED WITH PERNICIOUS ANEMIA

Report of a Case

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THE OCCURRENCE of mental symptoms associated with pernicious anemia has been noted ever since the original description of the disease by Addison in 1848.[1] Minor mental manifestations are fairly frequent. Goldhamer and co-workers,[2] in an extensive study of the neurologic changes in pernicious anemia, noted irritability in 64 per cent, memory disturbances in 60 per cent and mild depression in 58 per cent of cases. More serious manifestations were less frequent. Delusions occurred in 18 per cent, coma in 18 per cent, hallucinations in 16 per cent, apathy in 6 per cent and maniacal outbursts in 2 per cent of cases. Mental aberration severe enough to be classed as psychosis was found in 15.7 per cent of patients with pernicious anemia by Herman and his co-workers.[3] They also reported that 0.08 per cent of nonalcoholic patients admitted to the psychiatric division of Bellevue Hospital had pernicious anemia. Bowman [1] found the same percentage of patients with pernicious anemia in routine admissions to the Boston Psychopathic Hospital.

No characteristic pattern of mental reaction has been attributed to pernicious anemia. In an analysis of 40 patients with psychosis and pernicious anemia, Herman and his co-workers [3] found four well defined

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From the Medical and Neuropsychiatric Services, Veterans Administration Medical Teaching Group, Kennedy Hospital.

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1. Bowman, K. M.: Psychosis with Pernicious Anemia, Am. J. Psychiat. **92**:2 (Sept.) 1935.

2. Goldhamer, S. M.; Bethel, F. H.; Isaacs, R., and Sturgis, C. C.: The Occurrence and Treatment of Neurologic Changes in Pernicious Anemia, J. A. M. A. **103**:1663 (Dec. 1) 1934.

3. Herman, M.; Most, H., and Jolliffe, N.: Psychosis Associated with Pernicious Anemia, Arch. Neurol. & Psychiat. **38**:2 (Aug.) 1937.

clinical types: (1) an acute confusional state, (2) a paranoid condition, (3) an affective reaction and (4) an organic deterioration type. Ferraro and associates,[4] after a study of the neuropathologic picture, stated the belief that the organic changes precipitated or sensitized one toward a psychosis, the type of which was predetermined by a psychologic or constitutional mechanism. The relation of the psychosis to pernicious anemia is difficult to evaluate. Patients with pernicious anemia are no less prone to incidental psychoses than are normal persons. The nonspecific role of anemia and arteriosclerosis must also be considered. Barrett noted that many of the patients had a psychopathic family history and expressed the belief that the anemia was probably an incidental occurrence. However, the coincidence of the two diseases and the well known association with posterolateral degeneration of the cord makes it likely that the two are interrelated. The prognosis for the mental symptoms is variable. Occasionally the mental state improves with improvement in the blood count.[5] However, in some cases the psychosis persists and may clear only after six to twelve months.[6]

The case to be presented is of interest since a review of the available literature describes no case in which electric shock therapy was used.

REPORT OF CASE

W. T., a white man, aged 53, a farmer and lumber mill worker, was admitted to the surgical service of the Kennedy Hospital on Nov. 6, 1948, because of abdominal pain and vomiting, of six months' duration. Bloating and fulness of the stomach had been noted for several years. A history of tarry stools was obtained. During the eight weeks prior to hospitalization the patient had lost 30 pounds (13.6 Kg.) in weight. Dyspnea had been present for one year. He also stated that he had fainted on several occasions for no apparent cause.

Physical examination revealed a mentally confused white man, who was emaciated and obviously anemic. The blood pressure was 100 systolic and 50 diastolic. The abdomen was flat but slightly tender to palpation over the right upper quadrant. The rest of the physical examination was not contributory.

Laboratory Data.—The blood count on November 9 revealed 1,110,000 red cells per cubic millimeter, 4.5 Gm. of hemoglobin per hundred cubic centimeters and 3,400 white cells, with a differential count of 57 segmented forms and 43 lymphocytes. Marked poikilocytosis was present. The urine was normal. Gastric analysis revealed no free hydrochloric acid after stimulation with histamine. The total serum protein was 6.0 Gm. per hundred cubic centimeters, with an albumin-globulin ratio of 1.7. The serologic reactions of the blood were negative. A

4. Ferraro, A.; Arieti, S., and English, W. H.: Cerebral Changes in the Course of Pernicious Anemia and Their Relationship to Psychotic Symptoms, J. Neuropath. & Exper. Neurol. **4**:217 (July) 1945.

5. Noyes, A. R.: Modern Clinical Psychiatry, ed. 3, Philadelphia, W. B. Saunders Company, 1948.

6. Rundle, R. W.: Progress in Neurologic Manifestation, Blood **1**:209 (May) 1946.

roentgenologic series of the gastrointestinal tract was unsatisfactory but demonstrated an irregularity of the greater curvature of the stomach, which suggested neoplasm.

Course in Hospital.—It was felt that the patient had a carcinoma of the stomach, and an exploratory laparotomy was carried out on November 12. The patient received 1,000 cc. of blood during the operation. No evidence of ulceration, bleeding or neoplasm was found. A Meckel diverticulum was removed. After operation the patient's confusion and mental symptoms persisted. Purpura developed. The patient received nine additional transfusions of blood during the first five postoperative days. On November 15 the mental state became worse and the patient became somewhat agitated. This condition progressed until the morning of November 18, when the patient appeared definitely psychotic. He complained that "they are trying to send me to the electric chair" and that "they are trying to get me to tell a lie." Because of the purpura, he was seen in consultation by the staff members of the hematology section; after studies of the blood and bone marrow, which showed macrocytosis and megaloblastic hyperplasia of the marrow, a diagnosis of pernicious anemia was made. The patient was transferred to the medical service, and treatment was started with 2 cc. (30 units) of liver U. S. P. daily. The blood count at this time showed 3,350,000 red cells per cubic millimeter; 10.8 Gm. of hemoglobin per hundred cubic centimeters; 2,600 white cells, with a normal differential count; 167,500 thrombocytes; a hematocrit reading of 30 per cent, and 0.4 per cent reticulocytes. The patient continued to be disoriented, confused and suspicious. He heard voices telling him that he was going to die. He became abusive to personnel in charge of his care and was hyperactive and belligerent. He was transferred to the neuropsychiatric service, where he remained agitated and said that people were plotting against him. He attempted self injury by striking his head against the wall. Liver therapy was continued, and the blood count became normal by November 29. However, the patient remained psychotic for a month after the blood picture had reverted to normal. A lumbar puncture showed no cells; the fluid gave a negative reaction for globulin and contained 69 mg. of sugar and 20 mg. of protein per hundred cubic centimeters. The Kolmer reaction was negative, and the colloidal gold curve was normal. Electric shock therapy was begun December 29. Definite mental improvement appeared after the third treatment. After a total of seven treatments, he became oriented and ceased to exhibit bizarre behavior; his judgment appeared to be normal, and, according to his family, his mental status was the same as it had been prior to the onset of his illness. A follow-up study four months later showed no relapse of mental symptoms, and the patient's general health remained good. He had continued under liver therapy and was able to do some work in his garden.

SUMMARY

A brief discussion of mental symptoms occurring with pernicious anemia is given. A review of the available literature showed no case in which electric shock therapy had been used in conjunction with liver therapy.

A case of pernicious anemia with psychotic reaction which was treated with electric shock therapy is reported. Prompt improvement was noted.

BEHAVIORAL AND PHYSIOLOGIC CHANGES UNDER STRESS AFTER OPERATIONS ON THE FRONTAL LOBES

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SINCE the publication by Freeman and Watts of "Psychosurgery," [1] which is the first extensive review of the subject of frontal lobotomy, three additional reviews have appeared.[2] The main questions for discussion have been (1) the therapeutic value of the procedure, (2) the nature of the psychologic changes produced and (3) the amount of intellectual deficit shown.

Recently, Rylander [3] and Malmo,[4] working independently, demonstrated a reduction in general intelligence following frontal lobotomy, and Malmo concluded that the present balance of evidence favors interpretation of the observed deficit in terms of a reduction in the patient's ability to maintain a set in the face of interference. A formulation of frontal lobe function was stated as follows:

> . . . The frontal association areas are concerned with the ability to adopt a set toward a goal, or an attitude of expectancy, and with the ability to maintain such a set or attitude in the face of interference, until the expectancy is confirmed or denied, or until the goal is reached or abandoned [page 560].[4]

One of the most general clinical changes following frontal lobotomy has been that of lowered anxiety level. Few objective studies of emotional reaction, comparable to the objective investigation of intelligence in neurosurgically treated psychiatric patients, have been published.[5]

From the Allan Memorial Institute of Psychiatry and McGill University.

1. Freeman, W., and Watts, J. W.: Psychosurgery, Springfield, Ill., Charles C Thomas, Publisher, 1942.

2. Fleming, G. W. T. H.: Prefrontal Leucotomy, J. Ment. Sc. **90**:486 (Jan.) 1944. Freeman, W., and Watts, J. W.: Prefrontal Lobotomy: Survey of Three Hundred and Thirty-One Cases, Am. J. M. Sc. **211**:1 (Jan.) 1946. Walker, A. E.: Psychosurgery: Collective Review, Internat. Abstr. Surg. **78**:1 (Jan.) 1944.

3. Rylander, G.: Personality Analysis Before and After Frontal Lobotomy, A. Research Nerv. & Ment. Dis., Proc. **27**:691, 1948.

4. Malmo, R. B.: Psychological Aspects of Frontal Gyrectomy and Frontal Lobotomy in Mental Patients, A. Research Nerv. & Ment. Dis., Proc. **27**:537, 1948.

5. Rinkel, M.; Greenblatt, M.; Coon, G. P., and Solomon, H. C.: The Effect of Bilateral Frontal Lobotomy upon the Autonomic Nervous System, Am. J. Psychiat. **104**:81 (Aug.) 1947.

It appeared reasonable to assume that the same factors responsible for reduction in intelligence might be operative in the relief of anxiety, which has been observed.[6] It seemed logical to suppose that such factors might also be involved in other changes which have been noted after operation (e. g., relief from obsessive-compulsive behavior and reduced reaction to intractable pain).

One may state the hypothesis that clinical improvements in psychiatric patients after operations on the frontal lobe may occur because of a reduced tendency to maintain set. One may view anxiety, for example, as an anticipation, or expectancy, of unspecified unfavorable events to come in the future. Similarly, obsessions may be viewed as mental sets, and compulsions, as motor sets. Set in relation to persistent internal painful stimulation occurs in the patient with intractable pain. By our hypothesis, one would predict that prevailing sets, represented by such neurotic symptoms as anxiety, obsessions and compulsions, are broken down, interrupted or, in short, interfered with by current stimulations and activities after operations on the frontal lobes. Stimuli and activities in the present have greater potency than internally produced stimuli from sets and expectancies. By the same hypothesis, one would predict that the patient with intractable pain [7] might react less strongly to the pain after operation.

The hypothesis assumes that operation on the frontal lobe increases the potency of change in exteroceptive stimulation relative to the strength of internally maintained stimulation from sets and expectancies. The present study was designed to test this hypothesis at a relatively simple level of reaction to stress. Stressful exteroceptive stimulation was presented by irradiating the forehead briefly with heat at intensities near the pain threshold. Instructions to the subject were designed to produce internally maintained stimulation, from the expectancy of irradiation, and from the set to withstand this stressful stimulation without drawing away.

METHODS

Subjects.—Data on our surgically treated patients are presented in table 1. The first 5 patients represented in the table were studied at length with procedures other than those dealt with in this paper. These studies have been reported earlier in a symposium on gyrectomy by Penfield[8]; Cameron and Prados,[9] and

6. Halstead's concept of "biological intelligence" as applied to the frontal lobes would appear to embrace both "intellectual" and "emotional" aspects of behavior (Halstead, W. C.: Brain and Intelligence, Chicago, University of Chicago Press, 1947).

7. Freeman, W., and Watts, J. W.: Pain of Organic Disease Relieved by Prefrontal Lobotomy, Journal-Lancet **250**:953 (June) 1946.

8. Penfield, W. G.: Bilateral Frontal Gyrectomy and Postoperative Intelligence, A. Research Nerv. & Ment. Dis., Proc. **27**:519, 1948.

9. Cameron, D. E., and Prados, M. D.: Bilateral Frontal Gyrectomy: Psychiatric Results, A. Research Nerv. & Ment. Dis., Proc. **27**:534, 1948.

Malmo.[4] In the earlier report by Malmo, additional data on some of the patients with frontal lobotomy were presented.

Seven patients were examined before and after operation in our standardized stress situation (table 2). One of these patients (case 2), tested before and after frontal lobotomy, had had a frontal gyrectomy earlier. In addition, 1 patient (case 6) whose preoperative test was made before final standardization of the procedure had a somewhat different test. Stimuli were milder, and the series was shorter

TABLE 1.—*Summary of Data on Patients with Frontal Lobectomy*

Case	Sex	Age	Main Symptoms (Preoperative)	Diagnosis	Operation
1	M	26	Inability either to concentrate or to work; suicidal attempt	Chronic anxiety neurosis with feelings of unreality	Bilateral frontal gyrectomy—mesial and lateral, anterior
2	F	36	Listlessness, fear of crowds and heights	Chronic anxiety neurosis	(*a*) Bilateral frontal gyrectomy, lateral (*b*) Bilateral frontal lobotomy
3	F	42	Compulsions and fear of contamination	Obsessive-compulsive neurosis	Bilateral gyrectomy—mesial and lateral
4	F	32	Fear of contamination; hand-washing compulsion; depressed; suicidal attempt	Obsessive-compulsive neurosis	Frontal gyrectomy—lateral
5	F	39	Gradually increasing compulsive hand washing for 6 years; personal neglect and gradual withdrawal from others for similar period; extreme irritability from noise	Obsessive-compulsive neurosis with schizophrenic features	Frontal gyrectomy—inferior (orbital)
6	F	40	Anxiety; somatic complaints; depression; suicidal tendency	Anxiety neurosis with reactive depression	Bilateral frontal lobotomy
7	M	54	Anxiety and somatic symptoms, principally related to gastrointestinal system	Psychoneurosis—anxiety state	Bilateral frontal lobotomy
8	F	34	Anxiety and depression	Psychoneurosis—anxiety state with depressive features	Bilateral frontal lobotomy
9	F	31	Anorexia nervosa; continual fatigue	Psychoneurosis—anxiety state	Bilateral frontal lobotomy
10	F	31	Apathy, seclusiveness, bizarre behavior; suicidal attempt	Simple schizophrenia	Bilateral frontal lobotomy
11	F	21	Depression; patient felt people were against her, laughing at her; inability to work; suicidal attempt	Adult maladjustment; anxiety hysteria with marked depressive and paranoid features	Bilateral frontal lobotomy
12	M	19	Ideas of reference and of control; seclusiveness; anxiety; irritability; inappropriate affect	Simple schizophrenia	Bilateral frontal lobotomy
13	M	29	Withdrawal; vagueness; irritability; preoccupation with incestuous matters	Hebephrenic schizophrenia	Bilateral frontal lobotomy

than the one later standardized. The procedure followed before operation was, of course, repeated in the first postoperative test, and the results in case 6 could not be averaged with the data for the 7 patients who had the standardized battery.

The preoperative and postoperative tests were carried out with a smaller physiologic battery than the one ultimately assembled. Thirteen patients who had undergone operation were finally tested with the full physiologic battery, as described in the section on procedure. A previous report[10] has dealt with

10. Malmo, R. B., and Shagass, C.: Physiologic Studies of Reaction to Stress in Anxiety and Early Schizophrenia, Psychosom. Med. **11**:25 (Jan.-Feb.) 1949.

the results obtained with 75 unselected psychiatric patients in the same stress situation employed here. From this group, 13 patients, each matching one of the surgically treated patients in age, sex and preoperative clinical picture, were selected. These patients were selected solely on the basis of their case histories, without knowledge of experimental data obtained from them. These nonsurgical patients served as matched controls, thus providing comparative data to supplement the comparisons of preoperative and postoperative scores. A more extensive battery of physiologic measurements was employed with the matched pairs.

Procedure.—Twelve standard pain stimuli, of brief duration, were presented to the forehead by means of a modified Hardy-Wolff thermal stimulator. After each stimulus the patient was asked two questions about the stimulus. Throughout the experimental session continuous recordings were simultaneously taken of the following: finger movement, muscle potentials from the neck, respiration, heart rate, galvanic skin response and frontoparietal electric potentials. A careful record of head movements was also kept. The patient was asked to press a finger

TABLE 2.—*Pain Test Schedules*

Case No.	No. of Preoperative Tests	Time Since Operation (Weeks)		
		Test 1	Test 2	Test 3
1	0	159 (f. b.)*	..	..
2	2†	5 (f. b.)	..	..
3	0	140 (f. b.)	..	..
4	0	123 (f. b.)	..	..
5	1	2	7	13 (f. b.)
6	1‡	10	34 (f. b.)	..
7	1	4	23 (f. b.)	..
8	1	4	16 (f. b.)	..
9	1	7	9	18 (f. b.)
10	0	8 (f. b.)	..	..
11	1	5	8 (f. b.)	..
12	1	3	4 (f. b.)	..
13	0	5 (f. b.)	..	..

* f. b. means full battery of physiologic measures.
† Tests administered prior to bilateral frontal lobotomy (136 weeks after bilateral frontal gyrectomy).
‡ Preoperative and first postoperative tests were an earlier form, which was later revised.

button when he felt that the heat on his forehead was about to become painful. He was instructed not to draw his head away from the heat. A more detailed account of the procedure has been given in previous papers.[11]

Treatment of Data.—Records of finger movement and muscle potentials were scored by dividing the record into a number of specified time intervals and noting the number in which marked increases in the level of activity occurred. For respiration, measurements reflecting unsteadiness and immediate disturbance caused by stimulation were made. From records of the heart rate the mean and the standard deviation for sixty samples taken during the test were determined. The standard deviation provided a measure of variability or unsteadiness in the heart rate. The galvanic skin response was scored by determining the mean percentage change in resistance on stimulation. An attempt was made to score the electroencephalograms for the blocking response of the alpha rhythm to stimu-

11. (*a*) Malmo, R. B.; Shagass, C.; Davis, J. F.; Cleghorn, R. A.; Graham, B. F., and Goodman, A. J.: Standardized Pain Stimulation as Controlled Stress in Physiological Studies of Psychoneurosis, Science **108**:509 (Nov. 5) 1948. (*b*) Malmo and Shagass.[10]

lation, but too few records were adequately scorable to permit the inclusion of electroencephalographic results in the present analysis.

The statistical technic employed for treatment of data was Fisher's t test. The conventional standard of 95 chances in 100 that a significant difference is present was employed as the criterion of statistical reliability.

RESULTS

COMPARISON OF PREOPERATIVE AND POSTOPERATIVE RESULTS

Finger Movement.—In table 3 the average scores for disturbance in finger movement are shown for each of the time segments into which the record was divided. The number of button pressures is also presented in the table. The mean total scores for the preoperative and for the first postoperative tests were almost the same (41.1 and 41.6). However, on the second postoperative test the score dropped to 31. This difference between the preoperative test and the second postoperative

TABLE 3.—*Mean Scores for Finger Movement* *

Time Segment	Pre-operative Scores	First Post-operative Test	Second Post-operative Test
30 sec. before stimulus	7.4	6.6	3.7
During 3 sec. stimulus	4.6	6.6	3.7
17 sec. after stimulus	7.0	8.6	6.2
10 sec. before question	6.1	5.0	3.7
30 sec. after question	10.4	9.4	9.0
No. of finger pressures	5.9	5.1	4.7
Total score	41.1	41.6	31.0
Composite score (sum of 1 and 4)	13.4	11.6	7.3

* Values for second postoperative test represent the average for 6 cases (cases 5, 7, 8, 9, 11 and 12). One postoperative test was given in case 2.

test was statistically reliable. The most striking evidence of a decrease in disturbance of finger movements after operation may be observed in the time intervals preceding stimulation or questioning. Here, the scores go steadily downward from 13.4, before operation, to 11.6, on the first postoperative test, to 7.3, on the last test. The difference between the first and the third mean scores was statistically highly reliable. The mean scores for the interval preceding thermal stimulation are plotted in chart 1.

Comment: In a previous study, with nonsurgical patients,[10] it was demonstrated that increased disturbance in finger movement is associated with anxiety. The present results show that finger movement tends to decrease after operation on the frontal lobe, particularly if time intervals which involve anticipation of stimulation or questioning are considered. The data may probably be interpreted as evidence of decreased anxiety after operation.

The absence of a significant change in finger movement on the first postoperative test is remarkable, considering the notable change in the

second postoperative test. The possibility that the change in the second test was due to adaptation is unlikely in view of the results with head movement, which showed no adaptation. Adaptation also tends to be ruled out as an explanation by the data from matched pairs, to be considered later. From our data, the phenomenon appears to be related to the factor of postoperative interval (time since operation), rather than to repetition of the test. The only patient (case 12) who was given the test twice during the first postoperative month showed no drop in

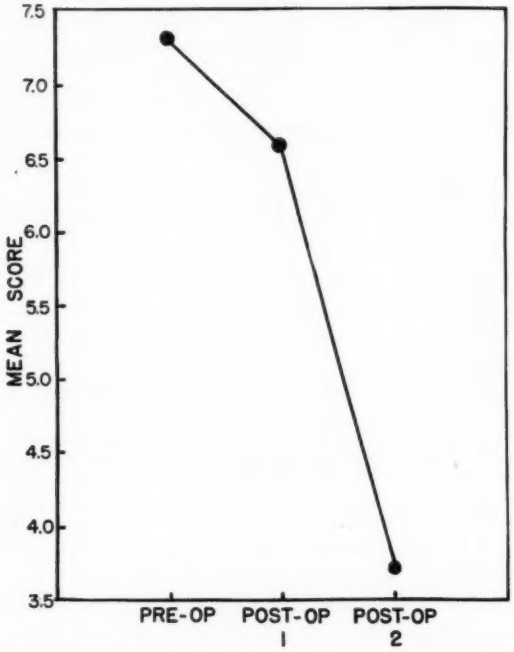

Chart 1.—Anticipatory finger movement: preoperative and postoperative comparisons of mean scores for disturbance in finger movement during a thirty second interval preceding a painful stimulus. The first postoperative tests were done at an average interval of one month, and the second test at an average interval of three months, after operation.

the score from the first to the second postoperative test. All the other patients were given the second test at least two months after operation, and in every instance the score for the second postoperative test was lower than that for the first. Evidence has been presented [12] which indicates that the patient is inclined to retain preoperative habit patterns

12. Porteus, S. D., and Peters, H. N.: Maze Test Validation and Psychosurgery, Genet. Psychol. Monogr. **36**:3, 1947.

for a short while, and that with the passage of time these habits become greatly weakened. Our findings may be interpreted as further evidence of this assumption. However, the point requires further investigation.

Head Movement.—Careful observations were made of the patient's head during the test. Withdrawal of the head consisted in drawing the head completely away from the optical chin rest. Any withdrawal of the head from stimulation was contrary to the instructions which were given the patient before the test began. Chart 2 shows that the mean

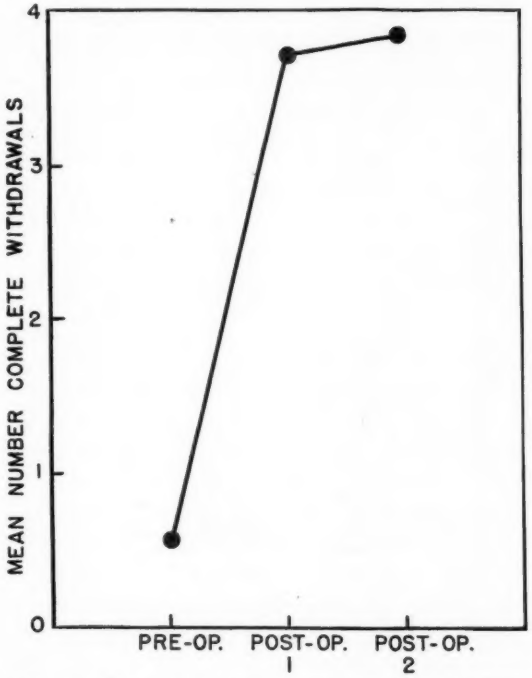

Chart 2.—Head withdrawal under stress during painful stimulation: preoperative and postoperative comparisons. The first postoperative tests were made at an average interval of one month, and the second tests at an average interval of three months, after operation. The curve represents the preoperative and the first postoperative score for 7 patients and the second postoperative score for 6 patients.

number of head withdrawals was much greater in both postoperative tests than in the preoperative test. The means for the postoperative tests (3.71 and 3.83) were both reliably greater than the mean for the preoperative test (0.56).

Comment: These results show the potency of exteroceptive stimulation in overcoming the subject's set to follow instructions not to with-

draw the head. Our findings here are in accord with those of Chapman, Rose and Solomon.[18]

Galvanic Skin Response.—Only 5 patients could be compared for the galvanic skin response before and after operation. In each instance the first postoperative record showed a higher mean percentage change in skin resistance in response to stimulation than did the preoperative one. The results for the 5 cases are shown graphically in chart 3. The mean percentage for the galvanic skin response was 12.3 before operation and 30.0 after operation. Owing to the small number of cases, this difference was not quite statistically reliable. However, the differences in all 5 cases were in the same direction, and the data suggest increased post-

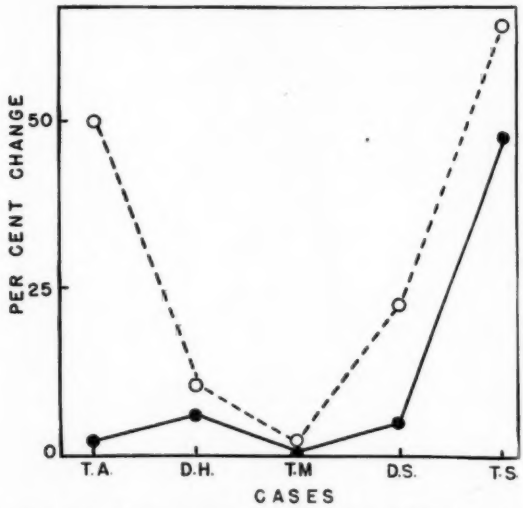

Chart 3.—Galvanic skin response: preoperative (solid line) and postoperative (broken line) comparisons of the mean percentage change in measured skin resistance following painful thermal stimulation. The average postoperative interval for the first test was one month.

The case numbers of the 5 patients are as follows: T. A., case 8; D. H., case 5; T. M., case 7; D. S., case 9; T. S., case 11.

operative reactivity of the skin in response to painful stimulation with the galvanic current.

COMPARISONS OF OBSERVATIONS ON MATCHED PAIRS

These comparisons included the full battery of physiologic measures. For nonsurgical patients the test constituted the first exposure to the stress situation. In the surgically treated group, the data in table 4

13. Chapman, W. P.; Rose, A. S., and Solomon, H. C.: Measurements of Heat Stimulus Producing Motor Withdrawal Reaction in Patients Following Frontal Lobotomy, A. Research Nerv. & Ment. Dis. Proc. **27**:754, 1948.

were derived from a first test in 5 cases, from the third test in 6 cases and from a fourth test in 2 cases. Data from tests conducted with part of the battery only are not presented.

Finger Movement.—The nonsurgical patients obtained a mean total score of 43.5, as compared with the mean of 33.3 for the surgically treated patients. The difference was reliable. It will be noted that the average score of 33.3 for this group of 13 surgically treated patients is very close to the value of 31.0 which was obtained in the second postoperative testing for the 6 patients who were tested before and after operation (table 3).

Comment: This finding lends further support to the conclusion that disturbance in finger movement is reduced after operation. In the presentation of preoperative and postoperative scores, it was noted that decreased disturbance occurred only on the second retest and that this may have been due to adaptation. Further evidence against this possibility comes from comparison of the scores for the 5 patients who had the test for the first time (mean score, 34.8) with the scores of the 8 patients who had the test for the third or fourth time (mean score, 32.4). The negligible difference observed here indicates that the effect of adaptation, if any, must have been slight.

Head Withdrawal.—The surgical patients drew their heads away from the stimulating heat twice as frequently as did the nonsurgical patients. The difference obtained here did not quite attain the criterion of statistical significance. However, when the score for the surgically treated group was compared with the score for a larger nonsurgical patient population (75 patients), a highly reliable difference was found.

Comment: Comparisons for the matched group support the results of comparisons of preoperative and postoperative scores for the same patient. It may be concluded that after operation on the frontal lobe the patients manifested an increased tendency to withdraw from the noxious stimulation, even though this constituted disobedience of instructions.

Muscle Potentials from the Neck.—Table 4 shows that the amount of disturbance in the record for neck muscle potentials tended to be greater for the nonsurgical patients than for the surgical ones. The difference was larger during the periods in which immediate reaction to painful stimulation would not be observable (preceding stimulation and before and after questioning) than during painful stimulation or immediately following it. However, the amount of disturbance in neck muscle potentials has been shown to be greatly influenced by the extent to which head movement occurs in reaction to stimulation. Consequently, since the surgical group displayed considerably more head movement, it would appear that tension of neck muscles, unrelated to withdrawal

of the head, was less in the surgical than in the nonsurgical group. To test this argument, we employed the data from a previous study,[10] in which the amount of head movement was related to the muscle potential score. From these data we determined the muscle potential score that would have been predicted for the surgical patients on the basis of the amount of head movement which they displayed. The mean predicted score was 16.3; the actual score was 12.3. The difference between the predicted and the actual scores was statistically reliable.

Comment: These determinations for the period of stimulation, taken together with the difference observed during the other periods, indicate that the surgically treated patients probably had less tension of the neck muscles than the nonsurgical ones.

Respiration.—No reliable differences in respiration were found.

TABLE 4.—*Comparison of Results for 13 Patients After Operations on the Frontal Lobes and for 13 Matched Nonsurgical Psychiatric Patients*

	Surgical Patients, Mean	Nonsurgical Patients, Mean	Reliability*
Finger movement (total score)	33.3	43.5	96
Head withdrawal	4.62	2.31	90
Muscle potential			
Score during and after stimulus	12.3	13.9	43
Score before stimulus, before question and after question	14.7	19.1	94
Respiration (percentage of deviation)	27.7	31.8	11
Respiration (irregularity on stimulation)	7.5	9.3	82
Mean heart rate	91.8	98.1	74
Variability in heart rate (standard deviation)	4.34	5.79	>99
Galvanic skin response (percentage change)	17.3	13.3	39

* The figures in the reliability column give the number of chances in 100 that the observed difference is a reliable one.

Heart Rate.—Mean Heart Rate: The mean heart rate for the matched patients was higher than that for the surgically treated patients, but the difference was not statistically reliable.

Variability in Heart Rate: The mean variability in heart rate for the surgical patients was less than that for the nonsurgical ones. The difference was highly reliable. The data for the individual matched pairs are shown in chart 4.

Comment: It thus appears that unsteadiness in heart rate under conditions of stress is diminished in patients who have had operations on the frontal lobe. The conclusion is further reenforced by comparing the scores for the surgical patients with the scores for the 75 nonsurgical patients; this comparison also yielded a highly reliable difference.

In our previous investigation with nonsurgical patients, it was shown that variability in heart rate tends to be greater in patients who present anxiety as a predominant clinical feature than in patients in whom anxiety

is less severe. The present finding may then possibly be taken as reflecting diminished anxiety in the surgically treated patients. From another point of view, the finding of diminished variability in heart rate leads one to consider to what extent the operation on the frontal lobe severed neural connections which influence the heart rate.

We also investigated the possibility that the observed differences were due to variation of heart rate in different phases of respiration. Heart rates were measured during inspiration and during expiration, and the differences in rate associated with respiratory phase were compared for the group of patients with operations on the frontal lobes and the 13 patients who were matched with them. In all cases the rate was higher during inspiration. The mean differences for respiratory phase

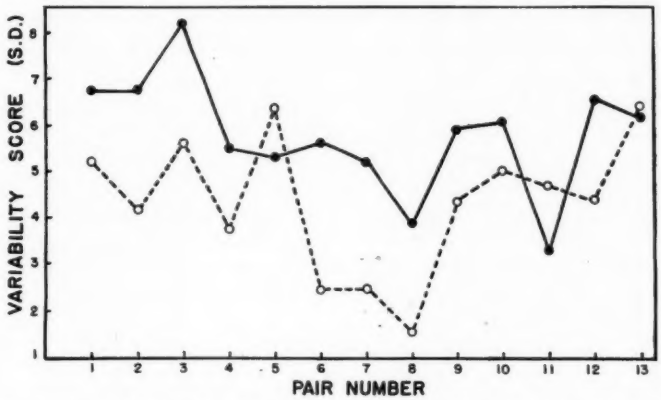

Chart 4.—Variability in heart rate. Comparison of scores for patients after operation on the frontal lobes (broken line) and scores for psychiatric patients not so treated (solid line) (matched pairs). *1*, case 8; *2*, case 6; *3*, case 13; *4*, case 10; *5*, case 3; *6*, case 5; *7*, case 2; *8*, case 7; *9*, case 1; *10*, case 9; *11*, case 11; *12*, case 4, and *13*, case 12.

were almost identical for the two groups, being 5.4 for the surgical and 5.2 for the nonsurgical patients. It was concluded that the difference in variability in the heart rate between these two groups could not be accounted for in terms of irregularities related to respiration.

Galvanic Skin Response.—No reliable differences with respect to the galvanic skin response were obtained. It should be pointed out that this result does not necessarily invalidate the tendency to greater postoperative response observed in the preoperative-postoperative comparisons, the reason being that through use of various other electrodes in recording the electrical conditions were altered. This point has been discussed more fully elsewhere.[10]

COMMENT AND CONCLUSIONS

In a setting of lowered tension and steadier heart rate, under stress, the patients who had undergone operations on the frontal lobes showed increased responsiveness to external stimulation. These findings support the hypothesis which the present study was designed to test.

Objective evidence of lowered tension after operation was found in the measurement of finger movement and in the measurement of muscle potentials from the neck. Muscular tension and steadiness of heart rate reflect the subject's physiologic state or the setting in which his responses to stimulation occur. Evidence that they may be to some extent an index of what one may call the "anxious set" was presented in a previous paper.[10]

In the present study, the increased potency of external stimulation was objectively demonstrated. After operation, withdrawal of the head from heat occurred more frequently, and the magnitude of the galvanic skin response was higher.

Thus, by means of objective behavioral and physiologic determinations, we have found differences which parallel the clinical observation that in some cases pathologic anxiety is reduced after operations on the frontal lobes. Moreover, it appears that such a change in psychiatric status may probably be understood in terms of the same formulation which was advanced to account for the observed reduction in intelligence following operative procedures on the frontal lobes.

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ELECTROENCEPHALOGRAPHIC STUDIES ON EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS IN RHESUS MONKEYS

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THERE are relatively few electroencephalographic studies on inflammatory and demyelinating diseases of the nervous system.

Berger [1] observed normal tracings in cases of epidemic encephalitis; his findings were corroborated by Schwab and Cobb.[2] Gibbs and Gibbs,[3] however, studying cases of severe acute encephalomyelitis, reported continuous slow waves which may be generalized over the entire cortex or located predominantly over a particular zone, thereby suggesting a focus. Lindsley and Cutts [4] observed a case of encephalitis in a 10 year old boy with repeated electroencephalograms. During the acute phase the record showed continuous slow activity; this abnormality gradually decreased to normal when the symptoms disappeared. Ross [5] noted large slow waves, often bilaterally synchronous, in 4 children with acute encephalitis and meningoencephalitis. These slow waves persisted beyond the acute phase of the disease and were not closely related to the severity of the clinical picture. In 240 cases

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1. Berger, H.: Ueber das Elektrenkephalogram des Menschen: III. Mitteilung, Arch. f. Psychiat. **94**:16, 1931.

2. Schwab, R. S., and Cobb, S.: Simultaneous Electromyograms and Electroencephalograms in Paralysis Agitans, J. Neurophysiol. **2**:36, 1939.

3. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Lew A. Cummings Company, 1941.

4. Lindsley, D. B., and Cutts, K. K.: Clinical and Electroencephalographic Changes in a Child During Recovery from Encephalitis, Arch. Neurol. & Psychiat. **45**:156 (Jan.) 1941.

5. Ross, I. S.: Electroencephalographic Findings During and After Acute Encephalitis and Meningo-Encephalitis, J. Nerv. & Ment. Dis. **102**:172, 1945.

of encephalitis, Gibbs and Gibbs [6] found a direct correlation between general severity of the symptoms during the acute and subacute phases of the illness and the degree of the electroencephalographic abnormality; the abnormality was also found to be frequently focal. In the postencephalitic syndrome, electroencephalographic abnormalities persisted only in cases in which seizures continued. The authors concluded that the electroencephalogram is of value in the diagnosis of acute encephalitis and of prognostic value for postencephalitic epilepsy. Marsh [7] reported that in 7 cases of encephalitis the "dysrhythmia" was usually severe—it might be focal, scattered or generalized. His data were essentially the same as those presented by previous authors.

In cases of meningitis, Gibbs and Gibbs [3] observed scattered slow waves even when the patient was fully conscious. Williams and Gibbs [8] noted high voltage, continuous slow waves and many wave and spike discharges in Schilder's disease (progressive subcortical encephalopathy). In patients with multiple sclerosis, Berger encountered electroencephalograms with scattered slow waves. However, Gibbs and Gibbs [3] reported that the electroencephalogram usually appeared normal in multiple sclerosis, even when the clinical picture was quite severe. Freeman and Cohn [9] found abnormal patterns in only 1 of 6 cases. On the other hand, Hoefer and Guttman [10] observed abnormal records in 44 per cent of a series of 107 cases of multiple sclerosis. In cases of athetosis and chorea, slow waves were found which in some instances subsided even though the disease persisted (Gibbs and Gibbs [3]). Bertrand, Delay and Guillain [11] reported a case of hemichorea with high voltage, slow activity over the affected side. In cases of parkinsonism, the electroencephalogram did not show any conspicuous changes (Gibbs and Gibbs,[3] Schwab and Cobb [2]). In a case of acute arsenical encepha-

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7. Marsh, C.: The Electroencephalographic Findings in Measles Encephalitis, Bull. Los Angeles Neurol. Soc. **13**:15, 1948.

8. Williams, D., and Gibbs, F. A.: Electroencephalography in Clinical Neurology: Its Value in Routine Diagnosis, Arch. Neurol. & Psychiat. **41**:519 (March) 1939.

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10. Hoefer, P. E. A., and Guttman, S. A.: The Electroencephalogram in Multiple Sclerosis, Tr. Am. Neurol. A. **70**:70, 1944.

11. Bertrand, I.; Delay, J., and Guillain, J.: L'electro-encephalogramme: normal et pathologique, Paris, Masson & Cie, 1939.

lopathy, Engel, Romano and Goldman [12] noted at the height of the reaction a record which they classified as borderline.

Pacella, Jungeblut, Kopeloff and Kopeloff,[13] employing intracerebral and peripheral injection of poliomyelitis virus in monkeys and guinea pigs, found that in the monkeys the electroencephalographic abnormality appeared only after paralysis had set in, whereas in the guinea pigs there were no abnormal electroencephalographic changes even after paralysis occurred. Records taken on 17 convalescent patients with severe residual paralysis yielded only 2 definitely abnormal and 5 borderline electroencephalograms.

In an attempt to clarify the origin of diffuse and disseminated encephalomyelitis, many clinical and experimental studies have been conducted following the lines of the original contributions of Putnam [14] on the value of venous thrombi. A possible allergic origin of these diseases has been under intensive investigation. In this connection, observations were made on the encephalitis of measles, of scarlet fever and of whooping cough and on encephalitis complicating vaccination and rabies treatment (Pette,[15] van Bogaert,[16] Ferraro [17]).

The first experimental approach was carried out in 1933 by Rivers, Sprunt and Berry,[18] who reproduced in monkeys a type of encephalitis and encephalomyelitis characterized by perivascular infiltration and demyelination by injection of various suspensions of brain. Rivers and Schwentker [19] and Ferraro and Jervis [20] confirmed their results. Using

12. Engel, G. L.; Romano, J., and Goldman, L.: Delirium: IV. Quantitative Electroencephalographic Study of a Case of Acute Arsenical Encephalopathy, Arch. Neurol. & Psychiat. **56**:657 (Dec.) 1946.

13. Pacella, B. L.; Jungeblut, C. W.; Kopeloff, N., and Kopeloff, L. M.: The Electroencephalogram in Poliomyelitis, Arch. Neurol. & Psychiat. **58**:447 (Oct.) 1947.

14. Putnam, T. J.: Evidences of Vascular Occlusion in Multiple Sclerosis and Encephalomyelitis, Arch. Neurol. & Psychiat. **37**:1298 (June) 1937. Putnam, T. J., and Alexander, L.: Disseminated Encephalomyelitis: A Histologic Syndrome Associated with Thrombosis of Small Cerebral Vessels, ibid. **41**:1087 (June) 1939.

15. Pette, H.: Die akutenzündlichen Erkrankungen des Nervensystems, Leipzig, Georg Thieme, 1942.

16. van Bogaert, L.: Les manifestations nerveuses au cours des maladies eruptives, Rev. neurol. **1**:150, 1933.

17. Ferraro, A.: The Pathology of Demyelinating Diseases As Allergic Reaction, Arch. Neurol. & Psychiat. **52**:443 (Dec.) 1944.

18. Rivers, T. M.; Sprunt, D. H., and Berry, G. P.: Observations on Attempts to Produce Disseminated Encephalomyelitis in Monkeys, J. Exper. Med. **58**:39, 1933.

19. Rivers, T. M., and Schwentker, F. F.: Encephalomyelitis Accompanied by Myelin Destruction Experimentally Produced in Monkeys, J. Exper. Med. **61**:689, 1935.

20. Ferraro, A., and Jervis, G.: Experimental Disseminated Encephalopathy in the Monkey, Arch. Neurol. & Psychiat. **43**:195 (Feb.) 1940.

the technic introduced by Freund and McDermott,[21] Morgan[22] and Kabat, Wolf and Bezer[23] obtained acute disseminated encephalomyelitis in rhesus monkeys after one to three injections of an emulsion of normal brain and liquid petrolatum U. S. P. falba® and heat-killed tubercle bacilli. The same result was described in rabbits by Morrison[24] and in guinea pigs by Freund, Stern and Pisani[25]; Kopeloff and Kopeloff[26]; Jervis and Koprowsky,[27] and Cazzullo and Ferraro.[28] Ferraro and Cazzullo[29] produced in rhesus monkeys a chronic stage of the diffuse encephalomyelitis with features that resembled clinically and histopathologically those seen in diffuse encephalomyelitis in human beings.

Sway-back, a congenital disease in lambs, characterized by ataxia, blindness, spastic paralysis and demyelination throughout the nervous system, appears to be the only spontaneous disease among animals which is somewhat similar to the disseminated encephalomyelitis and multiple sclerosis in human beings.

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21. Freund, J., and McDermott, K.: Sensitization to Horse Serum by Means of Adjuvants, Proc. Soc. Exper. Biol. & Med. **49**:548, 1942.

22. Morgan, I. M.: Allergic Encephalomyelitis in Monkeys in Response to Injection of Normal Monkey Cord, J. Bact. **5**:614, 1946; Allergic Encephalomyelitis in Monkeys in Response to Injection of Normal Monkey Nerve Tissue, J. Exper. Med. **85**:131, 1947.

23. Kabat, E. A.; Wolf, A., and Bezer, A. E.: Rapid Production of Acute Disseminated Encephalomyelitis in Rhesus Monkeys by Injection of Brain Tissue with Adjuvants, Science **104**:362, 1946; The Rapid Production of Acute Disseminated Encephalomyelitis in Rhesus Monkeys by Injection of Heterologous Brain Tissue with Adjuvant, J. Exper. Med. **85**:117, 1947. Wolf, A.; Kabat, E. A., and Bezer, A. E.: The Pathology of Acute Disseminated Encephalomyelitis Produced Experimentally in the Rhesus Monkey and Its Resemblance to Human Demyelinating Disease, J. Neuropath. & Exper. Neurol. **6**:333, 1947.

24. Morrison, L. R.: Disseminated Encephalomeylitis Experimentally Produced by the Use of Homologous Antigen, Arch. Neurol. & Psychiat. **58**:391 (Oct.) 1947.

25. Freund, J.; Stern, E. R., and Pisani, T. M.: Iso-Allergic Encephalomyelitis in Guinea Pigs After One Injection of Brain and Mycobacteria in Water-in-Oil Emulsion, J. Immunol. **57**:179, 1947.

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27. Jervis, G., and Koprowsky, H.: Experimental Allergic Encephalomyelitis, J. Neuropath. & Exper. Neurol. **7**:309, 1948.

28. (*a*) Cazzullo, C. L., and Ferraro, A.: Production of Experimental Allergic Encephalomyelitis in Guinea Pigs via Intraperitoneal Route, J. Neuropath. & Exper. Neurol. **8**:70, 1949; Isoallergic Encephalomyelitis Produced in Guinea Pigs via Intramuscular and Intraperitoneal Injection of Antigen, Arch. Path. **48**:316 (Oct.) 1949.

29. Ferraro, A., and Cazzullo, C. L.: Chronic Experimental Allergic Encephalomyelitis in Monkeys, J. Neuropath. & Exper. Neurol. **7**:235, 1948.

As far as we know, no electroencephalographic studies have been conducted either on animals with sway-back or on animals with experimental encephalomyelitis. We considered it of interest, therefore, to study the electroencephalograms of monkeys in which diffuse encephalomyelitis was produced by means of injections of an emulsion of normal brain and adjuvants. The animals were studied clinically during the acute and subacute phases of the disease and recordings taken in these various stages.

MATERIALS AND METHODS

Twenty-two rhesus monkeys [29a] were given injections of an emulsion of normal brain and adjuvants, in accordance with Freund's technic. Two types of emul-

Data on Experimental Allergic Encephalomyelitis in Monkeys

Monkey	Emulsion Strength	Amount, Cc.	Number of Injections	Interval Between Injections, Days
1	2	1	2	45
2	2	1	3	15
3	1	1	2	7
4	1	1	1	..
5	2	1	2	7
6	2	1	5	5
7	1	1	4	7
				Interval 55
			8	7
8	1	1	2	15
10	2	0.25	2	15
11	2	0.5	9	15
12	2	0.5	2	7
				Interval 28
			3	7
14	1	1	2	15
15	2	0.125	3	15
				Interval 45
			2	15
16	2	0.25	2	15
				Interval 67
17	2	0.125	6	7
18	2	0.25	4	15
19	2	0.125	3	15

sions were employed: The first (strength 1) contained 0.2 Gm. of normal monkey brain and 0.5 mg. of heat-killed tubercle bacilli per cubic centimeter, and the second (strength 2) contained 0.05 Gm. of normal monkey brain and 0.1 mg. of heat-killed tubercle bacilli per cubic centimeter. The emulsions were prepared with falba® [30] as an emulsifying agent. The tubercle bacilli were previously incorporated in liquid petrolatum U. S. P.[31] and then added to the normal brain suspended in 10 per cent isotonic sodium chloride solution U. S. P.

The intervals between injections were generally five, seven and fifteen days. In some instances in which symptoms had not developed after the first course

29a. Dr. A. Ferraro made available to us the experimental animals.

30. Falba® is an absorption base derived from hydrous wool fat U. S. P. and composed of oxycholesterol and cholesterols.

31. The paraffin oil (liquid petrolatum U. S. P.) was of low specific gravity.

of injections, the monkeys were subjected to a second, similar course. All the injections were given intramuscularly in the arms and legs. One group, of 5 monkeys, were subjected to a prolonged series of injections into the muscles of the chest. The amount of the first injection was 0.5 cc. of a 1: 100,000 solution of the original strength 2 emulsion, the series being continued with two injections a week, the concentration of the dose being increased to 1: 50,000, 1: 25,000, and so on, until it reached 1: 8.

All the animals were examined neurologically before treatment, and no abnormal signs were elicited.

The electroencephalograms were taken by means of a two channel Rahm apparatus with six needle electrodes placed over the frontal, motor and occipital areas bilaterally. The animal was blindfolded and restrained to a board; a head-holding attachment was utilized to immobilize the head. No drugs were found necessary to quiet the animals. Tracings were recorded from all animals prior to the treatment and repeated at intervals during the course of the disease.

OBSERVATIONS

Although the symptoms varied considerably, the clinical features characteristically indicated widespread involvement of the central nervous system. The pyramidal (motor) system, as well as the vestibulocerebellar system, was always involved, in varying degrees, although the vestibulocerebellar system was generally predominantly affected.

Our material may be classified under the following diagnostic categories: (1) the vestibulocerebellar syndrome with pronounced ataxia, dysmetria, dyssynergia, nystagmus and tremor of varying intensity; (2) a mixed syndrome with predominantly motor disturbances, such as hemiparesis, which sometimes ended in tetraparesis (animals with this syndrome had more convulsions than the others, which were often localized at first and then became generalized); (3) the lethargic-ophthalmoplegic type, which was usually fatal in a relatively short time; (4) the syndrome of optic neuritis, which resulted in atrophy of the optic disks, frequently with associated symptoms referable to the vestibulocerebellar and motor pyramidal systems.

When the neurologic and optic symptoms of the encephalitis were fluctuating for several days, the animals recovered quickly or died suddenly. In the event of recovery, although the neurologic symptoms cleared up, the visual symptoms persisted, with atrophy of the optic disk. Convulsions usually occurred during the early phase of the disease only.

NEUROPATHOLOGIC STUDIES

Complete neuropathologic studies were made on only 3 animals of this series. The following staining methods were employed: Nissl's, Holzer's, Spielmeyer's, hematoxylin and eosin, Roizin's combined method, Cajal's gold chloride–mercury bichloride method and Hortega's silver carbonate method.

Grossly, the brain did not reveal appreciable changes in most instances, but showed slight thickening of the meninges and occasionally mild diffuse hyperemia. Histologically, the common feature of the pathologic process was a diffuse inflammatory reaction, affecting almost all areas of the central nervous system, from the forebrain to the spinal cord. However, the cerebellar and vestibular regions, as well as the structures of the brain stem, were extensively involved.

The meninges and the gray and white matter showed the presence of perivascular exudates in various stages of formation, ranging from mild infiltration with lymphocytes and polymorphonuclear leukocytes to a prominent perivascular cuffing and occlusion of the blood vessels. In some areas the dominant cells were lymphocytes; in others compound granular corpuscles were present.

In general, the nerve cells were not severely affected, although they occasionally showed acute degeneration and pyknosis. The alteration of the nerve cells was not as great as that of the other structures. The glial reaction was observed in various phases. Frequently hypertrophy, and sometimes hyperplasia, of the astrocytes was seen. In some cases, as described by one of us (C. L. C.) in a previous paper with Ferraro,[28a] a process of gliosis of some degree, usually focal, was observed.

The pathologic lesions were either diffuse or focal, involving most frequently the cerebral white matter of the cortex. The perivascular infiltration and the demyelination were the main features. Axis-cylinders were well preserved in the less affected areas, whereas all stages of pathologic change were noted in areas of major inflammatory reaction and destruction of the myelin.

COMMENT

There appears to be a rough correlation between the electroencephalographic tracings and the clinical symptoms. In most animals evidence of electroencephalographic disturbance preceded the appearance of clinical symptoms. The focal findings in the electroencephalogram corresponded with the clinical localizing signs. In animals with convulsions the interseizure electroencephalogram contained "convulsive" discharges, similar to those seen in monkeys with experimental epilepsy and in epileptic patients. Immediately preceding and after the actual convulsions, tracings showed the usual characteristic patterns (spike and discharges and slow activity). The abnormality of the electroencephalogram was relatively pronounced in the acute stages of the disease and was frequently present even after the acute episode had subsided. Furthermore, the abnormality of the electroencephalogram became severer when a new acute episode occurred. In the cases in which the first acute outbreak was followed by substantial recovery, the electroencephalographic abnormality eventually cleared up almost completely but reappeared as soon

as a new episode began. In these cases the electroencephalographic disturbance also preceded the appearance of the clinical symptoms of the new acute episode. We were unable to find any definite correlation between the optic symptoms (blindness) and the electroencephalographic records.

The electroencephalograms of 2 animals did not correlate very closely with the clinical features. In 1 of these animals the neurologic signs were not prominent, but death occurred soon after a grand mal attack; the electroencephalogram for this monkey was of a borderline character throughout the period of observation.

In another monkey the electroencephalograms were taken shortly before the beginning of an acute episode and then later, when the animal was attaining a good recovery with no neurologic signs. The electroencephalographic records revealed no abnormality at any time. We should like to point out that on the whole these electroencephalographic disturbances were not very pronounced, a feature which may be related to the fact that the pathologic lesions were scattered chiefly in the subcortex of the brain, with relatively less involvement of the cortex, although there was a rough correlation between the electroencephalographic abnormality and the intensity of clinical symptoms.

SUMMARY

Clinical neuropathologic and electroencephalographic observations were conducted on 22 rhesus monkeys in which disseminated encephalomyelitis followed injection of an emulsion of normal monkey brain plus adjuvants.

A direct correlation existed between the clinical features and the electroencephalographic observations; the more intense the clinical symptoms, the severer the electroencephalographic abnormality. In the main, however, the electroencephalographic disturbances were of only moderate character, even in the cases of severe clinical disturbance.

The clinical symptoms consisted chiefly of ataxia, the tremor of paralysis and blindness in varying degrees. The lesions were largely distributed throughout the vestibulocerebellar and motor pyramidal systems.

GLOSSOPHARYNGEAL NEURALGIA ASSOCIATED WITH CARDIAC ARREST AND CONVULSIONS

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GLOSSOPHARYNGEAL neuralgia, while occurring with much less frequency than trigeminal neuralgia, is not a rare disease, and its classic symptomatology is well known. The first case reported was that of Weisenburg [1] in 1910. In 1924 Adson [2] reported 4 cases, in all of which the condition was treated by extracranial avulsion. However, since this was a difficult surgical operation, Adson described and suggested intracranial section of the nerve. In 1927 Dandy [3] first reported 2 cases in which cure was obtained by intracranial section through a unilateral cerebellar approach.

Spurling and Grantham [4] reviewed the literature in 1942 and reported a single case with separate trigger points in the throat and the ear. It was clearly demonstrated by them that with two trigger zones section of the upper two strands of the vagus nerve is essential for relief of symptoms.

Anatomically, the glossopharyngeal nerve is a mixed nerve, arising as several fibers from the rostral portion of the dorsolateral sulcus of the medulla. Leaving the medulla, the isolated root fasciculi, about six in number, assemble to form a single trunk, which traverses the foramen lacerum posterior in its own dural sheath, lying lateral and anterior to the tenth and eleventh cranial nerves.[5] Sensory branches

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3. Dandy, W.: Glossopharyngeal Neuralgia (Tic Douloureux): Its Diagnosis and Treatment, Arch. Surg. **15**: 198 (Aug.) 1927.

4. Spurling, G., and Grantham, E. G.: Glossopharyngeal Neuralgia, South. M. J. **35**: 509, 1942.

5. Piersol, H.: Human Anatomy, Philadelphia, J. B. Lippincott Company, 1936.

of the ninth nerve are distributed to the tympanic cavity and associated air spaces and to the mucosa of the upper portion of the pharynx, the tonsil, the soft palate and the palatine arches. Other branches reach the papillae of the posterior third of the tongue supplying taste. Motor branches are given off to the superior constrictor muscle of the pharynx and to the stylopharyngeus.

Sheehan and associates [6] found that afferent fibers arising from sensory organs in the carotid sinus pass centrally as the carotid sinus nerve, join the glossopharyngeal trunk and establish central connections with the vagus nerve, which is the efferent limb of the carotid sinus reflex arc. The significance of an irritable carotid sinus as a cause of syncope associated with fainting and convulsions was described by Weiss and associates [7] in 1933. Since that time surgical treatment of a hypersensitive carotid sinus has been directed toward intracranial section of the glossopharyngeal nerve. Results have been uniformly good.[8]

The fact that syncope and cardiac arrest are sometimes associated with glossopharyngeal neuralgia was first mentioned by Riley and associates [9] in a brief report at the annual meeting of the American Neurological Association in 1942. Their patients apparently were not subjected to operation. A case has been reported recently by Ray and Stewart [10] in which typical attacks of glossopharyngeal pain were accompanied with bradycardia, asystole and syncope. Intracranial division of the ninth nerve resulted in complete cure.

The occurrence of convulsive seizures in association with glossopharyngeal neuralgia has not been previously noted, although seizures have been observed as part of the carotid sinus syndrome.[7] In the

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10. Ray, B. S., and Stewart, H. J.: Glossopharyngeal Neuralgia: A Cause of Cardiac Arrest, Am. Heart J. **35**: 458, 1948.

case to be reported, convulsions were so significant a part of the clinical picture that they almost obscured the underlying etiologic factor.

REPORT OF A CASE

A white housewife, aged 72, was admitted to the medical service of Barnes Hospital on Sept. 9, 1947. Twenty months prior to admission she first experienced severe paroxysmal pain in the left side of her throat. Episodes of pain disappeared spontaneously after one month. She was free from pain for a year and a half, until one month prior to admission, when she was thought to have pharyngitis and was treated with penicillin and sulfanilamide. Pain subsided for several days under this treatment, but then returned. About ten days later she began to have convulsive seizures, characterized by twitching of the mouth, clonic movements of the arms and upward deviation of the eyes. The convulsions lasted only a few seconds. On the day prior to admission she knocked over a steam kettle during a convulsive episode and burned her left flank, thigh and arm. Numerous convulsive episodes followed, and hospitalization was advised by her local physician.

On detailed questioning, it was found that just prior to onset of the convulsions she had sudden severe, burning pain in the throat and at the base of the tongue, always on the left side. There was no pain in the ear. Within a few seconds after onset of the pain, convulsions with loss of consciousness occurred. There were forty to fifty such attacks daily. Because of the pain, the patient had eaten very little for a month.

Physical examination revealed that the patient was acutely ill with signs of recent loss of weight. She was drowsy and apathetic, but responded slowly to questions by shaking her head and would cooperate by turning when asked to. When urged to talk, she spoke in a whisper. There was a second degree burn of the left forearm, the left lower part of the abdomen and the left hip. The patient was edentulous. Her tongue was dry and cracked, and the anterior and posterior pillars and the posterior pharyngeal wall were moderately injected. There was a small amount of whitish exudate on the left tonsil, but no other abnormality was found in the nasopharynx. The blood pressure was 110 systolic and 60 diastolic. The heart beat was regular, with a rate of 64. Examination of the lungs revealed a few moist rales at the bases. The peripheral vessels were sclerotic and retinal vessels were narrowed. Neurologic examination showed nothing abnormal except for slight flattening of the right nasolabial fold and nystagmus on right lateral gaze; hearing was somewhat diminished on the left. The tendon reflexes were hypoactive, but equal on the two sides. During the examination she uttered a sharp cry, fell back unconscious on the pillows and exhibited clonic movements of the upper and lower extremities. The eyes turned upward. The episode lasted only a few seconds. Routine laboratory tests and spinal fluid studies gave normal results. Roentgenograms of the skull revealed no abnormality.

During her course in the hospital, the pulse rate varied between 50 and 70. An electroencephalogram showed a diffuse mixed dysrhythmia compatible with a convulsive state. She was placed under treatment with parenteral administration of fluids and was given phenobarbital sodium and diphenylhydantoin sodium U. S. P. (dilantin®). She gradually improved but continued to have occasional episodes of severe pain in her throat and ear, associated with convulsions.

She was seen by one of us (I. L.), who reproduced the pain and convulsions by stimulation in the region of the left tonsil. These responses were abolished

after cocainization of this region. It was suspected that the pain was glossopharyngeal neuralgia, but she was much improved and was discharged from the hospital, under the care of her local physician. She was readmitted to the hospital ten days later because of exacerbation of her attacks. The findings on general physical and neurologic examinations were the same as on the previous admission.

On Sept. 30, 1947, an electrocardiogram was made, first, during a free interval and then during an attack, which was produced by stimulation of the left tonsillar region (fig. 1). With the onset of the attack of pain, there was pronounced slowing of the pulse, which eventually resulted in a period of complete asystole

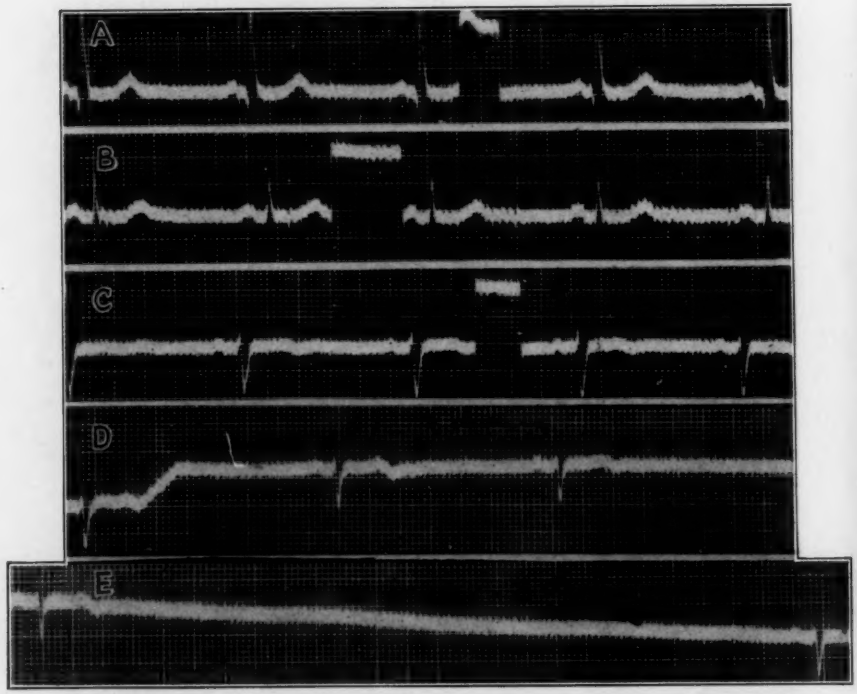


Fig. 1 (September 30).—*A*, *B* and *C*, An electrocardiogram taken during an interval between attacks, showing regular rhythm with left axis deviation. The heart rate is 50. *D*, electrocardiogram taken during an attack of pain initiated by mechanical stimulation of the left tonsillar fossa. Note the slowing of the rate, which progressed to complete asystole for six seconds (*E*).

for as long as six seconds before ventricular escape occurred. It was during the period of marked cardiac arrest that the patient had convulsive movements and loss of consciousness. Mechanical stimulation of the carotid sinus repeatedly failed to induce cardiac arrest or syncope.

The patient was subsequently transferred to the neurosurgical service, where, on September 30, section of the glossopharyngeal and the most rostral two stands of the vagus nerve was performed (Dr. H. G. Schwartz). Operation was per-

formed with the use of local anesthesia; stimulation of the ninth nerve resulted in pain in the throat, radiating to the ear. At the moment of section of the nerve the patient complained of severe pain, but immediately after the incision pain in the throat disappeared and she began to talk normally. In a similar manner, the rostral roots of the vagus nerve were stimulated and pain was referred to the ear, which the patient stated was not the same as her original pain. This seemed to indicate that the entire source of the pain was glossopharyngeal; but, in order that we might be certain of the result, the two most rostral roots of the vagus nerve were sectioned.

Except for some nausea and vomiting during the first two postoperative days, the patient did well. She began to take fluids and food without any discomfort

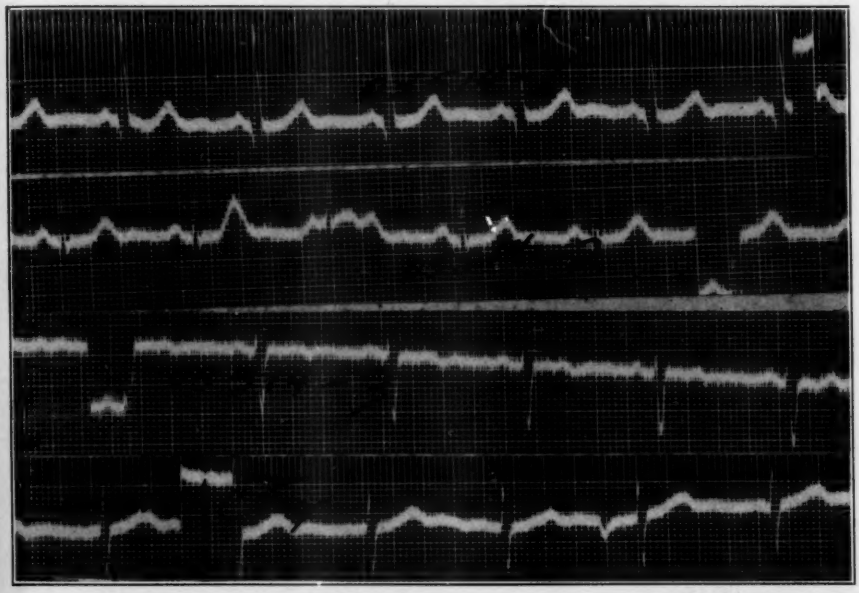


Fig. 2 (October 13).—Electrocardiogram taken thirteen days after operation. The heart rate is 69; the rhythm is regular. The left axis deviation persists, but stimulation of the tonsillar region does not produce slowing or asystole.

and rapidly regained her strength. She immediately became alert, and after operation her pulse never dropped below 60. There were no further convulsive seizures. At the time of her discharge, fifteen days after operation, the neurologic status was entirely normal. She has been followed for twenty months and has had no recurrence of pain, syncope or convulsions.

COMMENT

There is little doubt that the pain in this case was typical of glossopharyngeal neuralgia. Not only was the distribution in the domain of the ninth nerve, but it was readily reproduced by stimulation of the

tonsillar fossa and was abolished by cocainization of this region. Final definite proof lies in the fact that pain, cardiac arrest and convulsions were abolished by intracranial section of the ninth nerve.

It is unfortunate that we were not able to ascertain accurately the amount of sensory deficit resulting from section of the ninth and tenth nerve fibers. Repeated attempts were made to map out the area of sensory deficit, but without success, since the patient continued to have an active gag reflex. She noted no subjective loss of sensation, and sensation in the external auditory canal was normal.

The mechanism of fainting and convulsions associated with carotid sinus hypersensitivity has been shown by Weiss and Baker,[7] Ask-Upmark[11] and others to be due to retardation of the heart rate and a fall in blood pressure, which results in cerebral anoxemia. The present case is of particular interest in that the patient had repeated convulsive seizures characterized by momentary loss of consciousness, upward deviation of the eyes and mild clonic movements of all extremities lasting for a few seconds, always preceded by pain in the throat. These episodes could be precipitated by stimulation of the tonsillar fossa but were not influenced by digital irritation of the carotid sinus region.

Ask-Upmark,[11] in a careful series of experiments, attempted to demonstrate direct connection between the fibers of the glossopharyngeal nerve and the vasomotor nerves of the cerebral blood vessels. He expressed the belief that such a connection might account for the syncope and convulsions which occurred in several of Weiss's[7] cases of hyperirritable carotid sinus without bradycardia. He found that, in general, changes in the pial arteries paralleled the response of peripheral vessels to changes in the blood pressure, indicating that alterations in the systemic circulation and the cerebral vascular system were controlled by the same mechanism. He was unable to demonstrate any direct vasodilating effect on the pial blood vessels by stimuli arising in the carotid sinus nerve.

It has been accepted that in cases of a hyperirritable carotid sinus the initiating stimulus may arise from the sinus itself, presumably at the distal end of the sinus nerve (nerve of Hering), which joins the glossopharyngeal nerve centrally. In the case which we present, it has been demonstrated that equally effective stimuli may arise from the tonsillar branches of the glossopharyngeal nerve. Since the impulses from both stimuli presumably travel along the same central pathway, affecting the efferent vagal fibers in the brain stem, it might be expected that the incidence of cardiac arrest and syncope would occur in cases of glossopharyngeal neuralgia more frequently than it does. It is con-

11. Ask-Upmark, E.: The Carotid Sinus and the Cerebral Circulation, Acta psychiat. et neurol., 1935, supp. 6, p. 1.

ceivable that some alteration is present in the brain stem before volleys of afferent stimuli can exert a clinically demonstrable effect through the vagal efferent fibers. As yet there is no clinical or experimental evidence that such an alteration exists.

SUMMARY AND CONCLUSION

A case of glossopharyngeal neuralgia is presented which is unique in that the pain was associated with syncope and convulsions, which temporarily obscured the correct diagnosis.

It has been demonstrated that syncope can occur from afferent stimuli arising in branches of the glossopharyngeal nerve other than that to the carotid sinus.

The mechanism of the syncope and convulsions is bradycardia, with a fall in systemic blood pressure and cerebral anoxemia.

600 South Kingshighway (10).

Case Reports

ABNORMALITY OF THE CAPILLARY NAIL BED

MARTIN CASTELLANOS, M.D.
HABANA, CUBA
and
WILLIAM C. GIBSON, M.D.
MONTREAL, CANADA

A case is reported of unilateral post-traumatic tremor with abnormal capillary forms in the nail beds of the fingers of the affected side only.

REPORT OF CASE

The patient, a miner aged 49, had an excellent record of work underground for twenty-two years. One year prior to admission, he sustained a blast injury to the right side of his head when he accidentally released a high pressure jet of air (100 pounds per square inch from a 2 inch pipe) a few inches from his right ear. He was blown a distance of 12 to 15 feet (3.6 to 4.5 meters) across a mine drift and landed unconscious on a pile of wet, soft "muck." The explosion of heavy charges of dynamite which he had just laid soon roused him, and he discovered that his nose was bleeding profusely and his clothes were covered with blood. He sought shelter from the falling rock and smoke of the explosions and, in a dazed condition, made his way along the drift to safety. Only after crawling 50 feet (15 meters) did he realize that his smashed miner's helmet and lamp were dragging behind him, still attached to his pocket battery.

There were no scars on the patient's face or body. No blood was coughed up or vomited. On washing his face in the mine shelter, the patient splashed water into his right ear, with severe vertigo resulting. He was kept off work by the mine physician, because of the danger of infection through the ruptured drum membrane on his descent and ascent on the deep mine hoist.

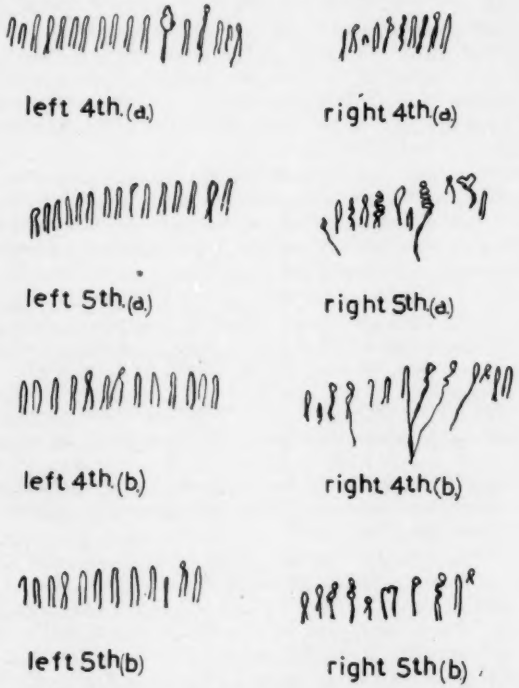
Within a month, the patient complained of vertiginous sensations when walking, of suboccipital headache and of weakness and tremor in the right arm and hand. After protracted examinations, the patient was given 3 per cent compensation by the Quebec Provincial authorities for the persistent tremor of the right arm. One year after injury, he was referred to the Allan Memorial Institute of Psychiatry, where examination of the capillary nail beds in his fingers revealed an unusual picture.

The study of the capillaries in the nail beds of the fourth and fifth fingers of each hand was carried out with a Zeiss microscope lens giving a magnification of 50 diameters, cedar oil being used to clear the skin. Transversely reflected light was used to illuminate the nail bed and corium. Criteria for the designation of abnormal capillary forms were drawn from the work of Cobb,[1] Haupt-

1. Cobb, S.; Cohen, M. E., and Badal, D. W.: Capillaries of the Nail Fold in Patients with Neurocirculatory Asthenia, Arch. Neurol. & Psychiat. **56**:643-650 (Dec.) 1946.

mann [2] and Paskind and Brown.[3] A second series of observations was made on the same fingers five days after the first.

As can be seen from the figure, the fourth and fifth fingers of the left (unaffected) hand showed a preponderance of normal capillary forms. On the first examination (*a*), the fourth finger exhibited only 3 abnormal capillaries in a total of 17 seen in one field, while the fifth finger showed only 2 abnormal capillaries in a field of 15. Reexamination (*b*) of the left hand five days later showed, in the fourth finger, 2 abnormal capillaries in a total field of 13 and, in the fifth finger, 2 abnormal, 1 doubtful and 9 normal capillaries.



Capillary forms in the nail beds of the fourth and fifth fingers of the left (normal) and the right (affected) hand as examined on two occasions (*a* and *b*) five days apart.

In the trembling (right) hand the findings were reversed. On the first examination, the nail bed of the fourth finger showed 6 abnormal, 1 doubtful and 3 normal forms. In the fifth finger there were 8 abnormal capillaries and only 3

2. Hauptmann, A.: Capillaries in the Finger Nail Fold in Patients with Neurosis, Epilepsy and Migraine, Arch. Neurol. & Psychiat. **56**:631-642 (Dec.) 1946.

3. Paskind, H. A., and Brown, M.: Constitutional Differences Between Deteriorated and Nondeteriorated Patients with Epilepsy, Arch. Neurol. & Psychiat. **49**:49-55 (Jan.) 1943.

normal ones. Five days later the nail bed of the fourth finger showed 9 abnormal and 4 normal capillary forms, and the fifth finger, 7 abnormal, 2 doubtful and 1 normal capillary.

Physical examination showed a well muscled, apprehensive man, with a gross tremor of the right hand, made worse on attention. Sensory examination showed hyperesthesia unrelated to neurologic segments, and great inconsistency and unreliability in two point discrimination in the right hand.

Psychologic examination revealed that "memory, not only recent, but also old recall, was defective. Rote memory was severely disturbed." Reexamination one month later showed "no improvement in the memory deficit."

Roentgenologic examination of the head and neck revealed no abnormalities. Electroencephalographic examination, with a basal skull lead, was similarly noncontributory. Otolaryngologic examination revealed a mixed middle ear–nerve deafness amounting to 40 decibels, with evidence of organic change in the middle ear and drum membrane on the right side. There was no clinical evidence of gross damage to the right internal ear.

The patient's tremor was relieved for ten minutes only after intravenous injection of 0.5 Gm. of amobarbital sodium (sodium amytal®). This remission was associated with voluble euphoria. The tremor was not modified by the intravenous injection of mephenesin ("myanesin"; 3-ortho-toloxy-1,2-propanediol).

A diagnosis of postconcussion syndrome was made.

The capillary forms seen in this case are in accord with the figures presented by Marinesco and Bruch,[4] which show grossly abnormal loop and syncytial forms in the affected limbs only in hemiplegic patients, both infants and adults, as well as with lesions of the brachial plexus.

University Hospital, Habana (Dr. Castellanos).

Allan Memorial Institute of Psychiatry, Montreal (Dr. Gibson).

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4. Marinesco, G., and Bruch, A.: Recherches de capillaroscopie et des troubles vasculaires dans quelques maladies nerveuses et des glandes à sécrétion interne, Presse méd. **38**:665-670, 1930.

News and Comment

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

The following candidates were certified at a meeting of the Board in Chicago, October 1949.

Psychiatry.—Carl P. Adatto, New Orleans; Harry Adler, Los Angeles; Ilka Wilheim Adler, Cleveland; Thomas H. Ainsworth, Fort Worth, Texas; Abraham Aronson, Elgin, Ill.; Charles T. Batten, Los Angeles; Benjamin J. Becker, Forest Hills, N. Y.; Anne Benjamin, Chicago; Henry Benjamin, Harding, Mass.; E. James Brady, Denver; Harry Brandman, Gary, Ind.; Frank A. Buell, Alhambra, Calif.; Henry Rives Coleman Chalmers, Atlanta, Ga.; Kenneth William Chapman, Bethesda, Md.; Loren E. Conner, San Diego, Calif.; Simon J. Conrad, Los Angeles; Oleinick P. Constantine, Waco, Texas; Alfred Edgar Coodley, Los Angeles; Victor John Covalesky, Scranton, Pa.; Charles B. David, Berkeley, Calif.; Robert Hugh Dickinson, Chicago; Richard E. Duisberg, Phoenix, Ariz.; Marion B. Durfee, South Pasadena, Calif.; LeRoy William Earley, Chicago; Henry H. Finberg, Chicago; Louis August Gottschalk, Chicago; Joseph Cook Grasberger, Perry Point, Md.; Max D. Graves, Pittsburgh; Paul Holley Gray, Baltimore; Michael B. Greenfield, Danville, Ill.; James Alexander Hamilton, San Francisco; Irene Anderson Harris, Norfolk, Va.; Henry M. Hawkins, North Little Rock, Ark.; Marc H. Hollender, Chicago; Connie I. Hood, Yakima, Wash.; William D. Horton, Seattle; Carl R. Jackson, Auburn, Calif.; William P. Kapuler, Brooklyn; Jack Munro Kenyon, Hartford, Conn.; Carl L. Kline, Milwaukee; John A. Kneipp, Natick, Mass.; *Heinz Kohut, Chicago; Joseph M. Krimsley, New York; Harold J. Lawn, Chicago; Marvin Walter Lathram Jr., Memphis, Tenn.; Stanley A. Leavy, New Haven, Conn.; Jerome Y. Lettvin, Manteno, Ill.; Israel H. Levin, Canandaigua, N. Y.; Jack B. Lomas, Beverly Hills, Calif.; Harold J. Madsen, Downey, Ill.; Vincent E. Mazzanti, Topeka, Kan.; John G. McGrath, Imola, Calif.; Stanley Theodore Michael, Garden City, N. Y.; Herman Nagler, Perry Point, Md.; Theodore C. Orlik, Coatesville, Pa.; Blake Daniels Prescott, Hartford, Conn.; Ernest A. Rappaport, Chicago; Joseph A. Rieger, Norman, Okla.; Joseph Robinson, Philadelphia; William H. Robinson III, Topeka, Kan.; Terry C. Rodgers, New York; Wendell H. Rooks, Wyckoff, N. J.; Moris Simon Rosen, San Francisco; Joseph Abraham Sampson, Agnew, Calif.; Roger F. Scherb, Camarillo, Calif.; Manuel Schreiber, Elgin, Ill.; John P. Shovlin, Waymart, Pa.; Sidney Harold Silver, Los Angeles; John P. Spiegel, Chicago; Mark L. Stone, Beverly Hills, Calif.; Harry Tabachnick, Milwaukee; Hyman V. Tavris, Los Angeles; Jack L. Tedrow, Salt Lake City; Sidney J. Tillim, Reno, Nev.; Mottram Peter Torre, New York; Charles William Umlauf, Philadelphia; Reber M. Van Matre, Oklahoma City; Harry H. Wagenheim, Lyons, N. J.; John J. Weber, New York; Daniel Marven Weiss, Dorchester, Mass.; Poe-Eng Yu, Middletown, Conn.

Neurology.—Milton Franklin Brougham, Wollaston, Mass.; Anthony R. Furmanski, Van Nuys, Calif.; Paul H. Garvey, Rochester, N. Y.; William Carleton Gibson, Vancouver, B. C., Canada; Louis Greenstein, Brooklyn; Donald W. Mulder, Denver; John A. Segerson, Topeka, Kan.

Neurology and Psychiatry.—Howard Krouse, Iowa City.

* The asterisk denotes complementary certification.

COURSE IN CLINICAL NEUROLOGY, UNIVERSITY OF MINNESOTA

A course in clinical neurology will be presented at the Center for Continuation Study, University of Minnesota, on Jan. 30 to Feb. 11, 1950. The course is intended for doctors of medicine who are interested in increasing their knowledge of clinical neurology. It is particularly recommended for neurologists, psychiatrists, pediatricians, internists and neurosurgeons. Visiting faculty members consist of Dr. Fred Mettler, Neurological Institute of New York and Columbia University, New York; Dr. Walter Klingman, University of Virginia Hospital, Charlottesville, Va.; Dr. Harold Voris, Mercy Hospital, Chicago, and Dr. Earl Walker, Johns Hopkins University School of Medicine, Baltimore.

HYGEIA BECOMES *TODAY'S HEALTH*

The trustees of the American Medical Association have authorized the renaming of the Association's health magazine, *Hygeia*. The new name will be *Today's Health*. The change will be made with the issue of March 1950.

DR. WARTENBERG HONORED

Dr. Robert Wartenberg, of San Francisco, has been elected an honorary charter member of the new Spanish Neurological Association and honorary president of the Inaugural Congress, to be held in Barcelona in December 1949.

FELLOWSHIP FOR ADVANCED RESEARCH IN GENETICS OR MENTAL HEALTH

Radcliffe College, Cambridge, Mass., invites applications for the Helen Putnam Fellowship for Advanced Research, open to postdoctoral women scholars in the field of genetics or of mental health, broadly defined to include such fields as clinical psychology and child development. Applicants should be prepared to submit a plan of research, and preference will be given to those whose research is already under way. The stipend will be $2,800 a year, with possibility of renewal. Application blanks may be obtained from the secretary of the graduate school, Radcliffe College, Cambridge, Mass. Completed applications should be returned not later than April 1, 1950.

Obituaries

IRVING HOTCHKISS PARDEE, M.D.

1892-1949

After an eventful, though a comparatively short, life, Irving Pardee died, a victim of acute leukemia, on April 10, 1949, at the New York Hospital, at the age of 57.

He came from a long line of physicians, his grandfather, his great-uncle, his uncle and his father, the late Ensign B. Pardee, having all embraced a medical career. His brother is the well known Harold E. B. Pardee, the cardiologist.

Irving Pardee graduated from Columbia University College of Physicians and Surgeons in 1912 and interned at St. Luke's Hospital, New York, and later at the Neurological Institute of New York, at which place he became senior intern of the Third Division, under Dr. Walter Timme.

At the outbreak of World War I he entered the Army as a first lieutenant in the Medical Corps. On his return, he engaged in research work in neurology and endocrinology and soon became associated with a group that specialized largely in endocrinology, then a rather new and suspiciously regarded field of medicine. He served in the endocrine clinic of the Neurological Institute for a number of years, transferring his activities later to the new Neurological Institute. He served as chief of clinic in that institution, conducting the clinic and supervising the classes in postgraduate work in endocrinology under the tutelage of Dr. Timme. Many of the physicians now practicing endocrinology in various neurologic and psychiatric hospitals throughout the country owe much of their success in this field to his instruction. His neurologic experience and writings began also to bear fruit, and he became a member of many general and local associations in his special fields. He was among the first to help in the organization of the Association for Research in Nervous and Mental Disease, of which he later became a vice president. He also became a member of the American Neurological Association, of which he was elected a vice president in 1942, and a member of the Association for the Study of the Internal Secretions, at which he read papers especially devoted to the so-called Cushing syndrome. He was elected chairman of the Section of Neurology and Psychiatry of the New York Academy of Medicine in 1937-1938 and president of the New York Neurological Society in 1947, was certified by the American Board of Neurology and Psychiatry and, of course, was a member of the American Medical Association.

He was the author of many papers on endocrinologic and neurologic topics.

Association with Irving Pardee was a pleasure and a delight; he was always cheerful under the most adverse conditions; he had a nimble and penetrating mind and, as a result, was an excellent diagnostician; he gave strict attention to his duties as attending neurologist at the Neurological Institute, as well as at St. Luke's, at which hospital he was director of the neurologic clinic. He became professor of neurology and executive officer of the department of neurology at Columbia University.

Dr. Pardee married Miss Margaret Trevor in 1917, the union producing three children, all of whom are married. Later he became divorced and married Mrs. Abby Rockefeller Milton, daughter of John D. Rockefeller Jr., who survives him.

Dr. Pardee's death was a great loss to medicine, especially in the fields of neurology and endocrinology. From an association with him for thirty-five years, the writer cannot recall a single instance of irritability or rancor even when disagreement and differences of opinion arose in such matters as the conduct of a case or the organization of a clinic. There was complete loyalty throughout his career, and his colleagues were at the same time his friends. All look back at their association with him with pleasure, tinged with regret at the loss of his companionship.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

AN EXPERIMENTAL STUDY OF THE RELATIONSHIP BETWEEN THE SIZE OF THE EYE AND THE SIZE OF THE OPTIC TECTUM IN THE BRAIN OF THE DEVELOPING TELEOST, FUNDULUS HETEROCLITUS. ELIZABETH LLOYD WHITE, J. Exper. Zool. **108**:439 (Aug.) 1948.

Two methods were used to study the effect of eyes on the size of the optic lobes of the brain. Surgical removal of the right eye in embryonic stages 16 to 22 of Fundulus heteroclitus resulted in 5 embryos with no right eyes and 8 embryos with reduced right eyes. By chemical methods (exposure of early embryos to dilute solutions of magnesium chloride, magnesium nitrate or alcohol), 108 embryos with one eye missing or reduced in size were obtained. These specimens were fixed at hatching, and the serial sections were studied. The results from the chemically treated embryos agreed in general with those obtained in the surgically treated embryos, but only the latter were used for measurements. Paper models of the eyes and optic tecta of 13 embryos were made and weighed. In 6 embryos cell counts of the gray matter of the optic tecta were made.

Removal of the right eye at stage 22 prevented the growth of retinal tissue, and no optic nerve was present. The embryos operated on at stages 16 to 20 developed varying amounts of retinal tissue, and an optic nerve grew from this into the brain at the normal point of entry.

Whenever the right eye was absent or reduced, the left tectum was reduced in size. The amount of reduction for the right eye ranged from 22 to 100 per cent, and that for the left tectum, from 2 to 25 per cent. On the average, reduction was greater when the eye and nerve were entirely missing than when some retinal tissue was present. However, if a reduced right eye was present with its optic nerve, there was no quantitative correlation between the amount of reduction of the right eye and that of the left optic tectum.

In most of the embryos with either no retinal tissues or reduced amounts of it on the right side, the reduction was greater in the cephalic half of the optic tectum than in the caudal half. In each of the 13 embryos the reduction of white matter was greater than that of the gray matter.

Cell counts indicated a greater amount of reduction than that obtained by the weighing of paper models. However, the distribution of reduction in the cephalocaudal direction was the same with the cell count as with the paper model–weighing method.

In this investigation the size of the eye, a peripheral sensory field, affected the number of cells in the optic tectum, perhaps by controlling the multiplication or degeneration of these cells. Results are discussed with reference to the "histogenetic gradient field" theory of Hamburger and Keefe, which was developed to explain the control by the peripheral motor field of the differentiation, but not the multiplication, of cells of the motor horn of the spinal cord in the brachial level of the chick.

REID, New Brunswick, N. J.

THE EFFECT OF TOTAL BRAIN ABLATION AT STAGE 28 ON SUBSEQUENT DEVELOPMENT AND BEHAVIOR IN TWO SPECIES OF AMBLYSTOMA. IRENE P. ANAGNOSTIS and ROBERTS RUGH, J. Exer. Zool. **109**:33 (Oct.) 1948.

Removal of the anlages of the major part of the brain of Amblystoma punctatum and Amblystoma opacum embryos by decapitation at stage 28 was followed by development of the remaining organs like that of intact, control larvae.

The external differences were: (*a*) absence of most of the organs associated with the head, although some mouth regeneration occurred; (*b*) long, feathery gills and multiple balancers, which were not resorbed during the period of these observations, and (*c*) development of a kyphosis, which in some cases was corrected as the animal grew in length.

In surgically treated A. punctatum larvae, response to hair loop stimulation occurred earlier than in controls. Locomotion in these experimental animals was initiated at the same time and with the same intensity as in the controls. However, as development proceeded, there was a rapid decline in the surgically treated animals.

In A. opacum embryos, although swimming responses began at the same time in both experimental and control animals, these reactions always remained at a low level in the experimental animals. Only in A. punctatum embryos was increased anesthesia time observed.

Serial sections confirmed the presence of the mouth and revealed variations in the amount of brain remaining (from none to portions of the rhombencephalon).

Although pigmentation was normal in early development, a general blanching of the skin and decrease in size of melanophores were apparent at stage 46.

The experiment was terminated one week after the controls had begun to feed because the experimental larvae lacked functional mouths and could not survive.

From these experiments, the authors conclude that early development, growth and differentiation of the main body systems in two species of Amblystoma can proceed completely without the higher centers of the central nervous system. Animals without forebrain, midbrain and hindbrain differentiated at a fairly normal rate, forming gills and forelimbs and such organs as heart and gut. In some of the A. punctatum series multiple and supernumerary balancers developed because of the disturbance of the anlage. Evidences of mouth regeneration were present in both species. There is confirmation of the conclusion that initial swimming responses are independent of the higher centers of the brain, which, however, are essential for the maintenance of normal motor activity.

REID, New Brunswick, N. J.

FIBRE CONNECTIONS OF THE SUBTHALAMIC REGION AND THE CENTRO-MEDIAN NUCLEUS OF THE THALAMUS. P. GLEES and P. D. WALL, Brain **69**:195, 1946.

Glees and Wall produced destructive lesions in the subthalamic regions in 5 macaque monkeys and killed the animals between twenty-one and thirty days later. The sections were stained with the Swank-Davenport technic. From these sections the authors were able to determine the projections of the subthalamic nucleus and the substantia nigra. The subthalamic nucleus was found to project to the external and internal divisions of the globus pallidus, to the ipsilateral and contralateral red nuclei, to the ipsilateral and contralateral thalami and to a nucleus dorsomedial to the substantia nigra. The substantia nigra was found to project to the globus

pallidus, the nucleus centromedianus and the anterior colliculus. In addition, Glees and Wall demonstrated a pathway from the centromedian nucleus and the dorsomedian nucleus of the thalamus to the central gray matter. This pathway traverses the subthalamic region.

FORSTER, Philadelphia.

Physiology and Biochemistry

EFFECT OF AMINO ACIDS ON THE FUNCTION OF THE MUSCLES OF PATIENTS WITH MYASTHENIA GRAVIS. CLARA TORDA and HAROLD G. WOLFF, Arch. Int. Med. **80**:68 (July) 1947.

Torda and Wolff report their findings on the effect of infusion of amino acids in patients with myasthenia gravis. Records of muscle action potentials were taken from healthy subjects and from patients with myasthenia gravis. The effect of amino acids were studied in 5 patients with this disease.

The authors state that their results suggest "that infusion of amino acids may augment the muscle action potential and improve the function of the muscles in patients with myasthenia gravis. General inferences may not be drawn from these results because of our inability to find a greater number of patients suitable for these particular electromyographic studies."

The mechanism of action of amino acids on muscle function in the aforementioned experiments is not yet established. Perhaps it is justifiable to point out that the described effect of the amino acids on the action potential may implicate several entirely different processes, i. e., (1) by supplying an essential amino acid to muscle or nerve, (2) by augmenting an as yet unidentified enzymatic process and (3) by increasing acetylcholine synthesis in a specific or nonspecific way. The last concept seems to the authors the most attractive, for the following reasons: 1. It has been demonstrated that in patients with myasthenia gravis there is a defect in acetylcholine synthesis. 2. Amino acids were found to increase acetylcholine synthesis in vitro. 3. The known decline of the amplitude of muscle action potential during prolonged stimulation of the motor nerve in patients with myasthenia gravis may be temporarily prevented by the administration of acetylcholine and neostigmine bromide. 4. An improvement in muscular function and muscle action potential followed the infusion of amino acids in the experiments presented here. It is therefore possible that the improvement in muscle action potential noted is referable to increased acetylcholine synthesis due to the administration of amino acids.

No therapeutic implications are justifiable from these preliminary experiments.

GUTTMAN, Wilkes-Barre, Pa.

ENDOCRINE REGULATION OF AMINO ACID LEVELS IN BLOOD AND TISSUES. F. FRIEDBERG and D. M. GREENBERG, J. Biol. Chem. **168**:405, 1947.

The amino acid concentration is highest in kidney and brain and decreases in other tissues in the following order: spleen, liver, testis and muscle.

PAGE, Cleveland.

THE PROJECTION OF THE FRONTAL LOBE ON THE HYPOTHALAMUS. ARTHUR A. WARD JR. and WARREN S. MCCULLOCH, J. Neurophysiol. **10**:309 (July) 1947.

Ward and McCulloch demonstrated corticohypothalamic connections by the method of physiologic neuronography. Area 6a of the cerebral cortex was found to fire the mamillary nuclei, the lateral hypothalamic area and the posterior

hypothalamic area; areas 8 and 10, the supraoptic nucleus; area 46, the paraventricular nucleus, and the orbital surface of the frontal lobe, the paraventricular nucleus and the posterior hypothalamic area.

Ward and McCulloch note that since the hypothalamic nuclei lie in a dense neuropil of fine, frequently unmedullated fibers one cannot conclude that the points of firing are necessarily the terminations of pathways.

FORSTER, Philadelphia.

EFFECT OF ULNAR NERVE BLOCK ON BLOOD FLOW IN THE REFLEXLY VASODILATED DIGIT. W. MELVILLE ARNOTT and J. M. MACFIE, J. Physiol. **107**:233, 1948.

Experiments are reported which show that ulnar nerve block does not significantly alter the blood flow of the fifth digit as estimated by calorimetry in normal human subjects in a condition of reflex vasodilatation. Local cooling of the fifth digit in subjects in this condition significantly lowers the blood flow, the degree of which is not further altered by ulnar nerve block. In brief, no evidence of specific vasodilator activity of nerve fibers was found.

It should be emphasized that this report deals only with the possibility of vasodilator fibers to digits. The observations of Grant and Holling (1938) afforded strong evidence of the existence of vasodilator fibers distributed to the skin of the forearm, and the investigations of Barcroft and Edholm (1945) provided physiologic proof of vasodilator fibers to muscle.

THOMAS, Philadelphia.

ROLE OF THE GLOSSOPHARYNGEAL NERVE IN THE CAROTID SINUS REFLEX IN MAN: RELIEF OF CAROTID SINUS SYNDROME BY INTRACRANIAL SECTION OF THE GLOSSOPHARYNGEAL NERVE. B. S. RAY, and H. J. STEWART, Surgery **23**:411 (March) 1948.

Ray and Stewart demonstrate that the decrease in pulse rate, fall in blood pressure and syncope produced by pressure over the carotid sinus in a series of 3 patients could be alleviated by intracranial section of the glossopharyngeal nerve on the side of the irritable carotid sinus. Fall in blood pressure on pressure over the carotid sinus after section of the glossopharyngeal nerve may be the result of occlusion of the carotid artery and resultant cerebral anoxia; the depressor type of sinus reflex may be the result of occlusion of the carotid artery in some cases. The response of the carotid sinus to chemical stimulation evidently is not mediated through the glossopharyngeal nerve and occurs despite blocking of the nerve. The authors believe that intracranial section of the glossopharygeal nerve is to be preferred to local removal of the nerve plexus because of absence of regeneration after section, freedom from danger of injury to the carotid artery and adaptability in cases in which conditions around the carotid sinus make local surgical procedures impossible.

FRANKEL, Philadelphia.

AUTOMATIC ACTS OF THE NEWBORN. ANDRÉ THOMAS and F. HANON, Rev. neurol. **79**:641 (Oct.-Nov.) 1947.

Thomas and Hanon report the study of the behavior of the newborn infant by motion picture analysis. Immediately after delivery the infant holds its arms in abduction in an attitude of crucifixion for a short time. The authors note that this has the effect of expanding the chest, as by the mechanism of artificial respiration, and is probably a response to anoxia. Standing responses and walking movements

can be elicited as early as the first day by supporting the trunk and taking care of coordination in the act of walking. The head flops loosely on the shoulders in an erect position but resists movements in various directions when the infant is horizontal. The trunk and the arms, which are kept usually in the fetal position, resist passive movement and restore themselves to this position. Various stimuli bring about quick extension of the arms from their normal resting position in the fetal attitude; this is the first part of the Moro reflex. The stimulus of altering the infant's position in space is apparently not sufficient to bring this about; backward displacement of the head is necessary, though the reaction has been brought about by other stimuli. The infant extends its arms and head in forcible crying. Once the reflex of arm extension has been elicited, it can be abolished by flexing the head on the trunk.

The authors note the complex synergistic response of the infant's mouth, lips, tongue, head and neck in orienting to the tactile stimulus on the face in the first part of the sucking reflex, which is completed by taking the stimulus object into the mouth. They note that the response started by the tactile stimulus cannot be considered a reflex, but, rather, as behavior oriented in time and space.

Further complex behavioral responses, such as the removal of a noxious stimulus from the foot by means of cross extension responses of the other side, are noted. Also noted is the constant response of incurvation of the trunk in response to stimuli in the lumbar region.

On the basis of this study, the authors point out the innate capacity of the infant for behavior oriented toward time and space from the very first hours of life.

LEGAULT, Washington, D. C.

Psychiatry and Psychopathology

THE MORPHOLOGICAL LEVEL OF PERSONALITY. J. M. TANNER, Proc. Roy. Soc. Med. **40**:301 (April) 1947.

Tanner, an anthropologist, analyzes two classifications of physique contemporaneously in use in England: Sheldon's and Cyril Burt's. Kretschmer's classification is considered obsolete because of his trimodal division into separate types, i. e., his failure to recognize the continuously varying components of body build unimodally distributed in the population. Sheldon, conceiving a variation along dimensional axes, began with a premise of continuous components; he disregarded size and found in a sample of 4,000 standardized photographs that each person had in his makeup some of each of three components (endomorphy, mesomorphy and ectomorphy); these components he rated on a scale of 1 to 7. His terminology of somatotype differs from the concept of the fixed type in being the result of the making of artificial discontinuities in a continuous scale. His gynandromorphic component concerns the degree to which the male body resembles the female, and vice versa, and is not entirely independent of the somatotype. By means of seventeen diameters of the body and the use of Sheldon's scale it is theoretically possible to determine objectively a person's somatotype. The basic objection to Sheldon's concept is that the original scale has been subjectively determined. A secondary objection is that the interpolation of values from anthropometry is uncertain.

The method of factor analysis used by Burt consists in "reducing a matrix of covariances or correlation coefficients, such as may be obtained from a series of measurements on the body, to a result of the linear combination of a few other,

mutually independent measures, called factors." The result is in terms of so much of factor A, so much of factor B and so much of factor C. The fundamental difference between Sheldon's method and this method lies in the fact that Sheldon's components are correlated whereas Burt's factors are not. Sheldon's scale, also, is uncertain.

In his investigation of personality from the standpoint of physique, the author uses the former term as referring to the sum total of all the attributes of a human organism, described at various levels, i. e., anatomic, physiologic and psychologic (including the levels of temperament, character, disposition and cultural behavior).

Factors derived from factor analysis cannot be taken to be anything more than principles of classification and cannot *a priori* be equated with physiologic or psychologic events, but they may on occasion represent the direct expression of a physiologic or psychologic event.

In studying the physiologic relations to Sheldon's components, the author, using 50 healthy students, found a positive correlation between ectomorphy and oral temperature and respiratory rate at rest, and a negative correlation with endomorphy ("spherical man in character"). Both ectomorphy and mesomorphy make for a higher oral temperature. This he considers one approach to "physiological anthropology."

A second approach is possible: the study of human growth or how the adult came to look that way. As Thompson states, "The form of an organism is determined by its rate of growth in various directions." Though the velocity of growth decreases from birth onward, two well defined periods of acceleration of growth are observed in hip width measurements—the adolescent spurt in girls from about 9 to 13 years of age and a smaller, midgrowth spurt between the ages of about 5½ to 7½ years.

The author analyzes some of the measurable components of growth and, on his premise that the clarification of the relation of physique and temperament will come about only on filling in the gap on the level between the anatomic and the psychologic, hypothesizes that Burt's factors can be identified with events occurring at certain times during growth. It is possible that these factors reflect the reactivity of a set of tissues at a particular time rather than the secretion of a particular hormone. The major control of these processes is genetic; how much environmental stresses at particular times can upset them is uncertain.

Sheldon's gynandromorphic component arises at the adolescent spurt, prior to which there is very little difference in growth pattern between boys and girls. In boys showing early spurt in growth the spurt has somewhat resembled the usual spurt of girls, but with late spurt the same similarity has been noted. It has been observed that boys with early spurt in growth have a higher degree of femininity than boys with a late spurt, this being at least a partial explanation of an observed relation between femininity of physique and behavior—a partial mechanism whereby some forms of homosexuality occur. "It seems that the way each tissue reacts to a hormonal stimulus common to all depends on its age."

BERRY, Philadelphia.

DIENCEPHALIC CRISES. C. I. URECHIA, Encéphale **38**:21, 1949.

Penfield was the first to describe under the term "autonomic diencephalic epilepsy" the disorder which Urechia has observed among the many varied disturbances in patients with paralysis agitans. The author was particularly struck by the sudden occurrence of crises of variable duration (from two hours to a day)

which disappeared as quickly as they appeared. The crises seemed to recall a sort of epileptic equivalent characterized by affective and vegetative disturbances and sometimes by a slight decrease in the patient's consciousness. The author describes 5 cases which he observed.

Case 1 was that of a married white man, aged 41, whose family and early history were without significance. There was no evidence of syphilis or alcoholism. He had grip in 1939. In 1942 there was onset of attacks of impulsive behavior, lasting about one hour, which the patient could master only with the greatest effort. His family became afraid of him and demanded his hospitalization. The physical and neurologic examinations revealed nothing remarkable. The spinal fluid findings were normal. There was no evidence of parkinsonism at the time of his admission. The crises appeared unexpectedly at almost any time, lasted from fifteen to thirty minutes and disappeared suddenly. During the attacks, the patient's face was congested, there was a rapid heart beat, the eyes shone brilliantly and his whole body was invaded by a feeling of restlessness and agitation. During the attack the patient became furious, destructive, argumentative and restless and had to be restrained. He also had an obsessive desire to kill any one around him. The patient tried desperately to control this desire but would become terribly afraid he would lose control and commit some crime. After the crisis had passed, he felt ashamed, regretful and fearful that perhaps he had committed a crime. During the intervals between seizures he was perfectly normal. The patient was observed in many such attacks. He never had amnesia for the crises. Four months after his first admission to the hospital oculogyric crises appeared and his face became masklike. The oculogyric attacks, while relatively rare, were usually accompanied with affective attacks. At times, however, the affective crises occurred without any accompanying oculogyric crisis. He was considered dangerous and was committed to an institution.

Case 2 was that of a white man aged 38. At the age of 31 he had encephalitis, and since the age of 35 he had shown parkinsonian symptoms. Neurologic examination revealed a classic picture of parkinsonism, with intermittent oculogyric crises, accompanied with diencephalic crises. With the appearance of the effective crises the patient would suddenly become sad, feel ill, seem apathetic and be fatigued. His heart beat rapidly; he sweated profusely and showed a tendency toward impulsive behavior and an impulsive desire to commit suicide which he fought with the greatest difficulty. The whole attack lasted ten or fifteen minutes, after which he begged for help because of fear of suicide. He left the clinic and a month later committed suicide at home during an attack.

Case 3 was that of a white man aged 43, with a history of encephalitis at 21. Since the age of 38 he had exhibited signs of a mild parkinsonian syndrome. For the previous three years diencephalic crises had appeared once a month. These attacks were characterized by rapid onset, depression, anxiety, clouding of consciousness and fear of something vague and indefinite which led him to seclude himself in his room. At times during the attacks suicidal tendencies appeared. His eyes often remained fixed in the same position for hours. There was a sensation of fulness and weakness, and he responded slowly and with difficulty to questions. He appeared absorbed and without initiative. The patient explained that the crisis began generally with the feeling of tension in the epigastrium and lasted several hours to a day or more. More recently the attacks had become more frequent, perhaps once or twice a week. Electric shock gave remarkable results. The crises became more infrequent, less intense and less prolonged. The patient felt well and was discharged.

Case 4 was that of a white man aged 41 who was hospitalized for parkinsonism of three years' duration. The parkinsonism was much more pronounced on the right side than on the left and was associated with oculogyric crises and sometimes with palpebral tics. The crises began with a feeling of great fatigue, anxiety and depression. During these attacks the patient spoke little, or not at all, responding only on great insistence. Everything around him appeared somber and altered; he felt as though he were about to fall asleep, and his state of consciousness seemed less clear than normal. During the crises he became obsessed with the idea that his wife was betraying him with a neighbor and that his son was dead. He thought also of suicide. He seemed to float in a waking dream but disliked being disturbed from it. This state would last from one or two hours, after which his mood changed, he begged for help and felt well.

Case 5 was that of a man aged 38 who showed parkinsonism with oculogyric crises and palpebral spasms. With the oculogyric crises, the patient appeared sad and preoccupied with his illness, complained of peculiar sensations and was often obsessed by suicidal ideas. The sudden onset and cessation of the attacks, and their other common characteristics, led Urechia to call this condition a type of diencephalic epilepsy, probably due to a disturbance of the diencephalohypophysial system. Vegetative epilepsy, as described by other authors, constitutes a disturbance in the same infundibular region. The author believes that his term "epileptiform diencephalic crises" is more appropriate. His observations lead him to plead for a separation of the diencephalic function into autonomic and affective. The diencephalic crisis in the cases reported was not followed by amnesia or convulsions. In patients with parkinsonism the crisis was often coincidental with oculogyric or palpebral attacks.

Autonomic epilepsy forms a transition between the diencephalic and the convulsive type of epilepsy. It is generally admitted, Urechia states, that epileptic attacks begin in the diencephalon and diffuse to the subcortical nuclei and to the cortex. Autonomic epilepsy may be considered as an epileptic attack limited solely to the diencephalon and not diffusing any further. In the autonomic type of epilepsy affective symptoms are absent or not pronounced. The author believes that the cases illustrate two disorders, epilepsy and parkinsonism, due to the same cause.

ZINKIN, New York.

Meninges and Blood Vessels

VALUE OF SPINAL FLUID EXAMINATION AS A DIAGNOSTIC PROCEDURE IN WEIL'S DISEASE. WALTER H. CARGILL JR. and PAUL B. BEESON, Ann. Int. Med. **27**:396 (Sept.) 1947.

Cargill and Beeson report the spinal fluid findings for 14 adults who had Weil's disease (spirochetal jaundice). Only 6 of the patients had clinical signs of meningeal irritation, and 13 of the 14 were found to have an abnormal spinal fluid. The commonest abnormality was an increase in the cell count. Xanthochromia was noted in approximately 90 per cent of the patients who had jaundice.

A survey of the literature on Weil's disease enabled the authors to obtain comparable data on 83 cases. Abnormalities of the spinal fluid were found in 83 per cent of these cases, but clinical signs of meningitis were present in only 41 per cent.

These observations indicate that studies of the spinal fluid assist in the early diagnosis of Weil's disease. This is important in view of the fact that there is no satisfactory test for this disease which is generally available or which gives a result quickly.

GUTTMAN, Wilkes-Barre, Pa.

Diseases of the Brain

MYOCLONUS. E. A. CARMICHAEL, Proc. Roy. Soc. Med. **40**:553 (Aug.) 1947.

Carmichael reports the case of a man aged 43 with normal past and family histories who at the age of 40 began to have infrequent generalized seizures, occasionally accompanied with focal sensory onset. As involuntary shaking movements of the legs progressed, the patient became bedridden in about two years. At the time of examination he had increasingly frequent involuntary movements of the limbs and trunk, initiated by minimal stimuli, interspersed with generalized sezures, progressive dysarthria, extreme weakness of the legs and slight weakness of the left arm, with incoordination of both arms.

Electroencephalographic studies demonstrated a large change in the potentials from the contralateral side of the scalp 3 to 5 cm. in front of the surface markings of the central sulcus near the midline when the leg was stimulated, or 5 to 8 cm. lateral to this point when the arm was stimulated, by any peripheral stimulus. The first stimulus of a series produced a spreading discharge, lasting up to one second, which was accompanied with a massive generalized discharge and jerking only in the segments stimulated.

BERRY, Philadelphia.

PAPILLEDEMA ASSOCIATED WITH CHRONIC BRONCHITIS, EMPHYSEMA AND POLYCYTHEMIA. MEADOWS, S. P., Proc. Roy. Soc. Med. **40**:555 (Aug.) 1947.

Bilateral papilledema with hemorrhages was the single finding on neurologic examination in a man aged 42 who had had chronic bronchitis and emphysema, associated with asthmatic attacks, for over twenty years. The spinal fluid pressure was 240 mm. of water. Ventriculographic studies failed to reveal signs of disease of the central nervous system. The peripheral blood showed polycythemia, with a red cell count of from 6,820,000 to 8,220,000 and a hemoglobin concentration of 116 to 134 per cent. The blood pressure was normal. Meadows stated the belief that the papilledema in this case was secondary to increased venous pressure and polycythemia caused by the chronic thoracic condition.

BERRY, Philadelphia.

PHENOMENON OF PHANTOM LIMB. B. BORNSTEIN, Encéphale **38**:32, 1949.

Bornstein bases his study of phantom limb on 28 civilians of whom 6 were women and 22 men. The ages ranged from 13 to 72 years, and the periods of observation, from one to twelve years. The second series of patients whom he observed were confined to a German camp for amputee prisoners of war during the recent war. Here, for several years he observed 1,700 amputees. The men drew pictures of their phantom limbs; some experiments on eidetic imagery were performed. The author lived with the men, knew them, talked to them and helped when he could. No surgical work of any type was done in the camp. The group consisted of men between the ages of 20 and 40. They were war wounded, only men with major amputations being kept there. In 50 per cent of the cases at least two of the larger articulations of the upper or the lower extremities had been amputated, some amputations being symmetric and some of all four limbs. Prosthetic work did not exist and general health and sanitation were bad.

The frequency of the apparition of a phantom limb was much higher than the 8 to 12 per cent usually given. In a great majority of cases, the imaginary limb began to be perceived several days after amputation. Usually in two weeks it was a well developed phantom. There were numerous cases in which the phantom did not appear until several years after the loss. The phantom appeared and disappeared

at various times during the patient's life. Sometimes the phantom appeared only for a few minutes before the patient fell asleep. There was no relation between the appearance of the phantom and age, sex, type of trauma, cicatrix or evolution of the wound. The length of time between injury and amputation made little difference. The element of mental shock played no role in the development of the imaginary limb. The most diverse mental influences contributed to the appearance, disappearance or transformation of a simple or algesic fantom.

There was considerable variety in the intensity and clarity with which the imaginary member was perceived, the different segments of the phantom member not being perceived with the same intensity. It was above all the distal parts or fragments which appeared most clearly. Often it was only a finger or toe which was felt clearly and intensely. Hunger, excitement, changes in weather, use of alcohol, fever and night intensified the perception of the phantom. The position of the body influenced the clarity of perception. The phantom was less clearly perceived while the patient was walking, and more clearly when he was lying down. It was generally declared to be most clearly perceived on the side on which the amputation had caused the more considerable loss. Bilateral phantoms were rare; the greater the number of amputations, the rarer the phenomenon.

The form of the imaginary limb generally corresponded to its real form with variations, particularly in the distal parts. The hand often appeared smaller, poorly developed, weak and useless. The size of the phantom usually corresponded to the real member, but the phantom was often perceived as shortened, especially in its long parts. This could be seen in the drawings of their phantoms made by patients. The author rejects Schilder's theory that the shortenings were based on childhood images. Rather, he found the shortening to be an expression of a compromise between the real member and its phantom perceived as partially mutilated. The phantom's position was generally presented in three ways: (*a*) as a limb hanging inertly along the body, as though in flaccid paralysis, and dragged passively by the movements of the rest of the body; (*b*) as a real limb, active, participating, assisting in balancing and supporting the gestures and movements of the other members, and (*c*) as perceived in some abnormal position making it troublesome and difficult to manage.

The sensitive, sensorial element of this phenomenon appeared under two forms, a nonpainful parasthesia and an algesic form *par excellence*. Sensations could be induced in the phantom by stimulating the collateral limb, by sticking a pin into the sound limb, and the like. Bornstein calls such phenomena allesthesia and interpreted them as an expression of hyperexcitability of the body image. He offers no explanation for the intense pains experienced in phantom limbs except perhaps that sympathetic fibers carry the stimuli to the central nervous system.

The author comments on the interpretation of the total phenomenon referred to as "phantom limb" as follows: It is dependent on and attaches to the mental existence of a body image. The idea of the limb is fixed in visual imagery in a fashion much closer than that in which the real limb is fixed and attached to the body. The image of the lost member can and does survive its material loss. If one were to localize the body image in the brain, it should be sought in the associative pathways which unite parietal and occipital areas with the subcortical centers (particularly the thalamus). The author believes that the investigations of Head, Gerstmann, Nielsen, Schilder and Reisner bear this out. He also feels that the visual type of person is predisposed to the perception of such phantoms. Therapy has been disappointing, but in 3 cases a series of two electric shock treatments gave favorable results. Such therapy should always be tried before recourse is had to lobotomy for intractable pain.

ZINKIN, New York.

Diseases of the Spinal Cord

CONCURRENT HERPES ZOSTER AND CHICKENPOX. FERDINAND FETTER and TRUMAN G. SCHNABEL, Arch. Int. Med. **83**:502 (May) 1949.

Fetter and Schnabel report the case of a white woman aged 72 who had herpes zoster on the right side, at the level of the eleventh and twelfth thoracic ganglia for five days prior to her admission to the hospital. A few days later she had a typical eruption of chickenpox, a disease she had never had previously. There was no history of recent exposure to chickenpox or of contact with a patient with herpes zoster. Within a week the generalized eruption of varicella had subsided. The cutaneous lesions of herpes zoster did not involute until almost two months after the onset, in spite of roentgen therapy and large doses of thiamine hydrochloride.

The authors cite reports of other observers which indicate that the viruses of herpes zoster and chickenpox are either identical or closely related. They state that "the simultaneous occurrence of the two diseases is presumably due to increased virulence of the virus, sufficient to overcome the patient's partial immunity to chickenpox."

GUTTMAN, Wilkes-Barre, Pa.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Dr. Charles L. Kubik, M.D., *Presiding*

Regular Meeting, Jan. 16, 1947

Endonasal Method of Operation on Pituitary Tumors: Report of Two Cases. Dr. OSCAR HIRSCH.

The 2 cases presented were the representatives of two series of cases of tumors of the pituitary gland for removal of which the endonasal method was strongly indicated or was the method of choice: a case of cystic tumor and another, of a chromophobic tumor, in a woman aged 75.

The first patient was a naval officer. His disease started, apparently in 1941, with vomiting, headache, decrease of function of the reproductive organ and with transient visual disturbance. This incident of visual disturbance repeated itsef three or four times within one year. He had been examined by two oculists, in 1941 and 1942; the findings were not significant. In March 1944, at the induction center, vision was found to be 20/20. In August 1945 hemianopsia had been found by examination at the Naval Hospital in Pearl Harbor. Since that time vision had become gradually worse. He had been treated by roentgen irradiation, but improvement was insignificant.

I saw the patient in my office in January 1946. There was bitemporal hemianopsia. The disks were pale, as a result of primary atrophy of both nerves. The roentgenogram showed enlargement of the sella turcica. The diagnosis of a tumor of the pituitary gland was certain. The patient, having been informed about the two operative methods, the cranial and the endonasal, chose the latter. I performed the operation in February 1946, with the use of local anesthesia. With one incision, a submucous resection of the septum was performed as far as the anterior wall of the sphenoid bone. The sphenoidal cavities were opened widely. The enlarged sella became visible. Its floor was partly destroyed and the remnants of its bony shell were removed. After incision of the tumor, dark red fluid began to drip under pulsation. The amount of the content could be estimated as 10 or 15 cc. The wall of the cyst, which was composed of dura, was destroyed by electrocautery to the point where it entered the sella. Vision improved gradually on the left side until it was close to normal; on the right side improvement was also noticeable, in spite of the bilateral atrophy of the disk.

A pituitary cyst like this one can easily be drained by the endonasal method, and a sufficiently large opening can be established to keep the cyst opened permanently. But even if the opening should close—which can happen with any method—the establishment of renewed drainage and the resection of the cyst wall is an easy procedure with the endonasal method, lasting only a few minutes. Seventeen per cent of all tumors of the pituitary body are cystic. The majority of these tumors betray themselves by calcification. In the absence of calcification, one can with some justification suspect a cystic tumor if the roentgen treatment is without result, as it was in this case.

For removal of the cystic tumors the endonasal method should be the method of choice. The patient ought at least to be informed about this operation. Removal of a cystic tumor by the endonasal method carries a very slight risk. I cannot recall that I have lost a patient with cystic tumor, even if I have had to operate on the patient several times, as happened in my early experience.

The next patient, a woman of 75, lost her eyesight gradually, first on the left side and later on the right. She consulted a neurosurgeon in 1945. He made the diagnosis of a tumor of the pituitary gland with homonymous hemianopsia in an advanced stage and advised roentgen irradiation. A pituitary tumor producing homonymous hemianopsia is difficult to reach by the intracranial method. The roentgen treatments were given in two series, several months apart. The first series achieved slight improvement for a short time. Therefore the second series was carried out, without benefit. When the patient came to consult me, she could not see fingers at a distance greater than 6 feet (180 cm), i. e., visual acuity was 20/200. With the left eye she could detect merely movements of the hand. Only the visual field of the right eye could be taken, and this showed temporal hemianopsia with sparing of the central area. In the left eye eccentric vision was noticeable for movements of the hand in the nasal field. I did not promise the patient any improvement from the operation, except in case the tumor was a cyst. The operation was performed four months prior to this report, with local anesthesia at first and thiopental anesthesia in the last stage. A solid tumor was encountered and removed as far as it protruded into the sella. Microscopic examination revealed a chromophobe tumor. Recovery was without event. The patient was discharged from the hospital in two weeks. After local application of radium, vision gradually improved from 20/200 to 20/70. The visual field broadened to a moderate extent. The patient can see again enough to write and to do needlework; she sees cars coming and going, and flowers and buds. Subjectively, the improvement is even better.

These cases represent two groups of tumors for which the endonasal approach is strongly indicated as the method of choice. The third group for which the endonasal method should be strongly considered is the intrasellar tumors, commonly found in cases of acromegaly, and in some patients with Simmonds' disease (hypopituitary cachexia). In about 50 per cent of all cases of acromegaly the condition is due to an intrasellar tumor. These growths can be called sphenoidal tumors, because they do not protrude into the cranial cavity. They are not visible in the cranial cavity. The neurosurgeon has to work with his instruments around a corner to reach them. In doing so, he may find the optic chiasm lying in his way. The endonasal method is independent of the relation of the chiasm to the pituitary tumor.

Recently I operated on 5 patients. They are all doing well. The number of cases of pituitary tumors in which I have used my endonasal method since 1919 is 242, with a mortality rate of 5 per cent. That was before the advent of the sulfonamide drugs and penicillin. One can expect that even this low rate may be decreased with these drugs.

The mortality in the operative treatment of pituitary tumors by the endonasal method is low for two reasons:

1. By the submucous resection of the septum a new pocket is formed which has no communication with the nasal cavity except for its first linear incision. Therefore, this pocket within which the operation is performed, and which leads to the sphenoid sinus and to the tumor, is comparatively free from bacteria.

2. The pituitary gland has no pia-arachnoid but is covered only by dura. Therefore, the operation on the tumor is extradural. That is obvious in the case of the intrasellar tumors. The deeper the tumor grows into the cranial cavity, the more it becomes covered by the pia-arachnoid, by the chiasm and by the ventricle. But still its intrasellar portion remains extradural, and only this part is the target of the endonasal operation.

This method was practiced by Cushing for eighteen years, and the results in most of his operations were excellent. The method has been somewhat neglected by the neurosurgeons. It requires, of course, a special technic.

DISCUSSION

DR. WILLIAM H. SWEET: We are grateful for another of Dr. Hirsch's valuable contributions to the therapy of sellar neoplasms. For my part, I have followed a highly conservative course in the selection of cases of pituitary adenoma for operation. Only in cases with extreme reduction of vision has a preliminary trial of roentgen treatment been rejected as the procedure of choice. The pressure of other work during the war accentuated my reluctance to operate in these cases. In a review of my material from January 1942 to January 1946, I find that I performed 402 major craniotomies, the overwhelming majority of which were for intracranial neoplasms in adults, but in that group were only 5 adenomas of the pituitary gland—less than 2 per cent. This percentage may be contrasted with Cushing's figure of 18 per cent in a series of 2,000 intracranial tumors. Although Cushing's material was heavily weighted with pituitary tumors because of his worldwide renown in treating them, the percentile difference remains tremendous.

Among my 5 cases of pituitary adenomas were 2 with massive extrasellar extensions, cases which Jefferson regards as usually unsuitable for surgical intervention. My experience would bear out this contention, since 1 patient died after operation and the other is worse fifteen months after operation than she was before it. The other 3 patients have maintained improvement and have been followed for from eighteen months to four years.

I am not at all certain that selection only of patients with the most advanced disease or of those refractory to roentgen ray therapy represents the proper treatment for pituitary adenomas. I find myself handicapped by the lack of statistics on the comparative long range results in terms of useful vision and ability to work for the three methods, namely, (1) Dr. Hirsch's method, (2) transfrontal intracranial operation and (3) roentgen therapy. There is a gap in the literature which needs to be filled by studies from clinics favoring each of these three methods.

DR. ROBERT S. SCHWAB: I am glad to have seen Dr. Hirsch's third patient. She was in our neurologic service this summer, when I was on visit. It was the consensus that we could not offer this patient neurosurgical treatment without undue risk. The medical consultants felt that, because of her age and health, she was too poor a risk. With her vision still failing, we were forced to offer her no hope. Roentgen treatment failed. It is gratifying to see the success of the endonasal operation in this case. The approach did not occur to us at the time as a possible compromise.

DR. HANNIBAL HAMLIN: I collaborated with Dr. Hirsch in the treatment of the first patient discussed, and I can assure you that I learned a great deal. His knowledge of the anatomy and pathology of the parasellar region is extraordinary. He has made this subject his avocation.

His method has a definite place in the treatment of pituitary tumors. As Dr. Sweet brought out, all three methods—the transfrontal, the endonasal approach and roentgen irradiation—have their place. The problem is to choose the suitable one. In Cushing's series of intracranial neoplasms, pituitary tumors occupied

second place. With inclusion of the craniopharyngiomas, they constitute a formidable group, and I am always apprehensive about such lesions. Cushing used the transphenoidal approach for many years. Henderson, in his review of 206 cases in which Cushing operated during the period from 1921 to 1931, endorsed the endonasal route as the method of choice for patients with hymonymous hemianopsia or unilateral blindness, in whom the chiasm is likely to be pushed up against the anterior communicating artery.

I think there are three reasons that the transphenoidal method has been forgotten: Primarily, Cushing abandoned it after six postoperative deaths from meningitis, an occurrence which is significant in view of present day chemotherapy. Second, with the transfrontal approach, vision was thought to have shown a more sustained improvement. Dr. Louise Eisenhardt, who has heard from the patients in Cushing's series of cases of pituitary tumors more recently than Henderson, told me that one of the most interesting developments in the follow-up observation has been the relatively good results with the endonasal approach; she stated that if Dr. Cushing were still operating he probably would have gone back to this technic when indicated. Finally, the method is one of selection and appears to be limited by sound advice based on specialization, which in this instance is concerned with the area between the floor of the sella turcica and the roof of the sphenoid sinus. We neurosurgeons should get together with Dr. Hirsch for better understanding of tumors of the pituitary gland and their surgical treatment.

Dr. James L. Poppen: Dr. Hirsch has devoted a great deal of time to this work, and he was one of the originators of this method. He deserves a great deal of credit. I agree that it is probably the method of choice for certain types of tumor. I disagree, of course, about the universal use of the transphenoidal operation. In the first place, one must always be certain that a patient with homonymous hemianopsia and unilateral erosion of the clinoid processes does not have a large aneurysm. That situation could better be dealt with intracranially. Another contraindication would be in the case of adenomas which have ruptured through their capsule. One sees many patients who have had roentgen therapy in whom the diaphragm of the sella has been ruptured laterally, posteriorly or anteriorly. If there is no rupture of the capsule and the tumor is cystic, choice of the transphenoidal route would be justifiable. The objection to operation on a cystic tumor by the intracranial route is not justified. Formerly, when a cystic tumor was encountered one merely evacuated it, and recurrence was frequent. Now one removes the cystic wall as completely as possible.

With solid pituitary tumors, the intracranial method is more thorough because evacuation of all the soft tissue and removal of the capsule from the roof of the sella, the internal carotid arteries, the optic nerves and tuberculum sellae are carried out. I wish Dr. Horrax were here, for we differ slightly as to the treatment of tumors of the pituitary gland. He follows up all his operations with roentgen irradiation, and I do not. We are running a parallel series. It is possible that roentgen ray treatment may be indicated, even though the tumor is removed. I think that a trial of roentgen treatment is of real value if the patient is watched closely with respect to visual fields and visual acuity. If there is no improvement within two to four weeks, the patient should have surgical treatment. My method would be intracranial. If the patient has a tremendous sella turcica, with the tumor ballooning into the sphenoid sinus, the transphenoidal approach may be the method of choice, if one is acquainted with the procedure.

DR. OSCAR HIRSCH: I wish to express my thanks to Dr. Sweet, Dr. Schwab and Dr. Poppen for their comments, and especially to Dr. Hamlin, whose remarks have been most valuable to me, since he was present at the operation in the first case I mentioned.

In answer to Dr. Sweet's question: I cannot cite the exact figures on the latest results in the intracranial and endonasal operations. I discussed the problem in detail before this society a year ago; therefore I did not bring slides with me this time. The operative mortality for the two methods is approximately the same, about 5 per cent. Of 39 patients from my earliest series, 23 have enjoyed the improvement achieved by the operation for ten to twenty years. Those with solid tumors receive an additional treatment with radium.

I did not know that the second patient had consulted Dr. Schwab; it is gratifying to hear Dr. Schwab's impression of the operation. In this case I could not remove much of the tumor. The tumor was inoperable by either the cranial or the nasal route. Only the sellar part was within reach of the instruments. This part was only the smaller portion of the tumor. A radium plate was applied beneath the tumor and to its frontal surface.

I need add nothing to Dr. Hamlin's appreciative words but my own—that, experienced as he is, he finds sufficient indication for the endonasal method.

In answer to Dr. Poppen: I should like to mention that I had an opportunity to watch Dr. Horrax and Dr. Poppen at work, and I greatly admired their skill. The greatest skill, however, cannot always overcome the obstacles due to the variable anatomic relations between the tumor and chiasm and the third ventricle. I shall show you a sagittal section of a pituitary tumor which has grown in both directions. It has filled and enlarged the sella and has also extended into the third ventricle. Such tumor cannot be completely removed, either by the intracranial or by the nasal method. By the former one is able to reach the central portion; by the latter, the lower portion. Both accomplish a decompression of the chiasm. Additional treatment is therefore necessary. The neurosurgeons use roentgen radiation; I myself radium—not the needles but a plate. This combination is only for tumors which cannot be completely removed.

The intrasellar tumors which do not protrude beyond the diaphragm are easily approachable by the endonasal method, whereas the intracranial method sometimes meets obstacles in the superimposed chiasm. The dissection of the chiasm is necessary in a case of this type. The cystic tumors, of course, can be operated on by either method. I would remind you that the reopening of a cystic tumor through the nose is very easy in case the cyst should refill.

Differential Spinal Block: III. Block of Cutaneous and Stretch Reflexes in the Presence of Unimpaired Position Sense. DR. STANLEY J. SARNOFF and DR. JULIA G. ARROWOOD.

This article was published in full in the *Journal of Neurophysiology* (**10**: 205 [May] 1947).

The effect of differential spinal block on the abdominal reflexes, patellar reflex and ankle clonus of 12 patients was studied in relation to the effect on motor power and the sensory modalities. Administration of the differential block consisted in the initial injection of 15 cc. of a 0.2 per cent solution of procaine hydrochloride, followed by injection of the same solution at the rate of 0.6 cc. per minute until the

desired block was obtained. The height and duration of the block desired determined the subsequent rate of administration. Determinations of skin temperature served as an index of vasomotor block; cessation of sweating, as an index of sudomotor block. The appreciation of pinprick; touch, position and vibration sensibility, and motor power were determined at five minute intervals.

It was noted (as it was in over 50 sets of previous observations) that fibers mediating vasomotor and sudomotor function and appreciation of pinprick were blocked, whereas touch, position and vibration sense and motor power were unimpaired. The abdominal reflexes disappeared concomitantly with the impairment of the appreciation of pinprick from the seventh to the twelfth thoracic dermatome. It was anticipated that, since position sense was unimpaired, the ankle clonus and patellar reflex would likewise be unaffected, as they are supposedly subserved by fibers of the same type. On the contrary, the patellar and ankle reflexes were among the first sensory modalities to be affected, and they were abolished in the absence of any ascertainable effect on position sense.

All previous data have been in accord with the thesis that the differential blocking effect is based on the axonal diameter and degree of myelination of the various types of fibers as they traverse the subarachnoid space. That is, the relatively small, unmyelinated fibers are susceptible to a lower concentration of procaine than are the larger myelinated ones. If the selective blocking effect on the afferent portion of the reflex arc subserving the patellar and ankle reflexes is based on this same principle, it must be concluded that the afferent fibers subserving the tendon reflexes are in the smaller, unmyelinated group and that they are distinct from the fibers subserving position sense.

In any case, it is convenient to introduce procaine into the spinal canal in such concentrations that it will be possible to examine critically intact position sense in the complete absence of tendon reflexes.

DISCUSSION

DR. D. DENNY-BROWN: Drs. Sarnoff and Arrowood have made an interesting observation which will undoubtedly intrigue physiologists. As Dr. Sarnoff has said the initial conclusion might be that the patellar reflex and ankle clonus are served by different afferent fibers than those of the proprioceptive sense of position and vibration. This would imply not only that the tendon reflexes are served by different sets of fibers from those which serve the latter sensations but that the kind of fiber is very different in diameter. Vibration sense appears to be an alternation of deep pressure sensations. It has been argued by some investigators that position sense is largely joint sense, served by encapsulated end organs that lie around the joints. Adrian and others have shown by sampling single afferent fibers that it is possible to trace sensation from movement to end organs in the joint capsule. Such discharges are haphazard and only approximately quantitative. Position sense in terms of quantitation is, however, a most accurate sensation. It is difficult to believe that the accuracy of appreciation of shoulder movement could be derived from end organs in the capsule of the shoulder joint. On the other hand, with denervation of the fingers it is difficult to estimate position of the terminal joints, so that here position sense is perhaps served by endings in the joint capsule rather than by tendon end organs. The afferent end organs in muscle can be classified as tendon end organs, muscle spindles, capsulated end organs of the pacinian or Meissner type, unencapsulated end organs and poorly medullated types

that appear to serve pain sensation. Tendon end organs and muscle spindles are supplied by afferent fibers, which are among the largest. In terms of conduction velocity and anatomic degeneration, they can be shown to belong to the largest of the alpha group. That leaves only stray corpuscles and end organs for pain, largely ramifying about the blood vessels. If proprioception sense is supplied by an end organ, there is at least a likelihood that it is supplied by large fibers corresponding in size to those that run into the dorsal columns and serve these sensations.

The ankle reflex is one of the most rapid in the nervous system. There is every reason to suppose that it has but one synapse, but it is also conducted with a minimal delay. It therefore should be supplied by a fiber of large diameter. The assumption is that it is related to muscle spindle end organs, although recently it has been shown to appear in development when the tendon end organ matures. There is considerable evidence that it is served by a large afferent fiber conducting at a high velocity.

Before one discards such physiologic evidence, one should consider the validity of the initial assumption made by Drs. Sarnoff and Arrowood regarding the action of the anesthetic on the nerve roots. It seems to me that the functions that are first disordered by injection of procaine into the subarachnoid space, namely, vasomotor function, pilomotor function, pain perception and cutaneous reflexes, are those that require a synapse in the spinal cord itself. There is good evidence that pain impulses undergo synaptic change within one or two segments. Is it possible that this anesthetic effect could be the result of cocaine affecting synaptic relations in the spinal cord, and perhaps later affecting nerve roots? All these functions are synaptic functions. The criterion for nonsensory function was a reflex, a vasomotor reflex or a tendon reflex. Also in favor of a hypothesis of synaptic interruption is the frequent finding in cords damaged by spinal anesthesia of lesions of the cord itself—of the gray and white matter—and not of nerve roots alone. There is occasional clinical evidence of persistent damage to the cord after spinal anesthesia. All this indicates not only that the anesthetic diffuses into the cord but that effective concentrations may reach the gray matter.

Dr. James L. Poppen: It would be folly for me to discuss this paper by Dr. Sarnoff and Dr. Arrowood after Dr. Denny-Brown's instructive discourse. I have just one point. In regard to his question of the synapses or of a difference in caliber of the nerve roots in relation to an anesthetic agent: We have made subarachnoid injections of absolute alcohol into the cauda equina. There were complete loss of sensation for a moment, or for a few minutes, and absence of reflexes. However, the motor power was intact. We have had several cases in which a metastatic lesion lay high in the thoracic region. I was called in on a case of intractable pain. I inserted a needle between the first and second thoracic spinous processes and injected 1 cc. of alcohol around the cord. There was anesthesia in four dermatomes, with no loss of motor power or interference with the reflexes or with position sense. The cord itself was not damaged by the absolute alcohol. This did not relieve the patient in any way, and so I introduced the needle into the substance of the cord. Then, of course, all sensation (transection of cord) was abolished.

Dr. Robert S. Schwab: I should like to ask Dr. Sarnoff whether he has read Jacobson's work on the patellar reflex. In normal people this reflex is lost in deep sleep, whereas in light sleep it is easily obtained. I believe this observation has been corroborated by electromyography, which showed that with Jacobson's method of voluntary relaxation of muscles in normal people the patellar reflex can be abol-

ished, although the subject has normal motor power and normal sensation. Jacobson expressed the belief that the patellar reflex requires a certain amount of muscle tone, I wondered whether Dr. Sarnoff and Dr. Arrowood considered the problem of muscle tone in their explanation of the loss of the patellar reflex.

DR. PAUL I. YAKOVLEV: Discussion being one of the purposes of a society, I should like to ask Dr. Sarnoff and Dr. Denny-Brown their opinion as to the validity of the following explanation of the loss of tendon reflexes without impairment of position sense in the course of rapidly developing analgesia from procaine introduced intraspinally and circulating about the dorsal roots.

The anterior horn cell lives in its "afferent environment," made up by stimuli constantly arriving to the cell via dorsal root fibers and via central fibers (corticospinal, tectospinal, reticulospinal, spinospinal, and so forth), all converging on the cell as the final common path. This afferent environment is highly specific. If one of its constituents is suddenly eliminated, the whole dynamic state of this environment changes, and the anterior horn cell may become, temporarily, refractory to all stimuli. This is known as a state of "shock," explained by von Monakow in his theory of "diaschisis" (*Gehirnpathologie*, Vienna, A. Hölder, 1905, page 240), and the explanation was accepted by Sherrington (the Integrative Action of the Nervous System, New York, C. Scribner's Sons, 1906, page 246). Thus, a slowly developing interruption of the corticospinal and of other descending central tracts to the anterior horn cell, as a result of a neoplastic or a degnerative process, does not abolish tendon reflexes; in fact, they tend to become exaggerated. On the other hand, it is a clinical fact of common observation that after a rapid interruption of the corticospinal tract as a result of a capsular hemorrhage or of thrombosis there is usually an initial period of flaccid paralysis with loss of all tendon reflexes; yet the position sense may be wholly intact. My question is this: Could not a similar refractory state of the anterior horn cell, without impairment of position sense, be induced as a result of a rapid and selective blocking of afferent fibers for pain in the dorsal roots? It would be interesting to know whether a gradual blocking of afferent fibers for pain with slowly rising concentrations of procaine would produce the same dissociation of position sense and tendon reflexes as those observed by Dr. Sarnoff.

DR. WILLIAM H. SWEET: Is this a pertinent observation? Absence of the ankle reflex is one of the commonest signs of a protuded lumbar intervertebral disk. That lesion is often unassociated with any loss of pain, touch, temperature or proprioception sensibility in the lower limb. In such cases the loss of the reflex is often due to pressure on a single nerve root. It is known from the work of Gasser and Erlanger that the largest, most heavily myelinated, fibers are the first to fail to respond when pressure is applied to a nerve trunk and is increased gradually. First, the A fibers, then the B fibers and, finally, the C fibers fail to conduct. That is, the undue pressure destroys function in fibers the sizes of which were in the reverse order of that which follows the application of noxious chemicals. In many of the cases of protruded intervertebral disk, then, there is an isolated loss of a tendon reflex, which, according to this interpretation of the selective action of the deleterious agent, pressure, would be more likely to result from involvement of the largest fibers than of the smallest fibers.

This type of clinical material leads one to a conclusion regarding the size of fibers concerned in mediation of the stretch reflex which is the reverse of that proposed by Drs. Arrowood and Sarnoff.

I wonder whether in the face of preservation of tactile and proprioceptive sensation, one is not forced to search for some other explanation of the absence of patellar and ankle reflexes. The tendon reflexes are responses which disappear clinically when a slight lesion is present. To revert to the example of a protruded intervertebral disk, I have always thought it remarkable that a laterally placed lesion at the fifth lumbar–first sacral interspace could cause an ankle reflex to disappear. The gastrocnemius-soleus muscle is supplied by three or four nerve roots, from the fourth or fifth lumbar down to and including the second sacral nerve roots. Nevertheless, severe compression of only the first sacral root by a protruded disk in the fifth lumbar–first sacral interspace commonly suffices not only to diminish but usually to eliminate the ankle reflex. Furthermore, this reflex is likely to remain absent for many months after removal of a lesion of the intervertebral disk—long after all other signs and symptoms have disappeared—additional evidence that the ankle reflex is a highly sensitive indicator of a lesion of the nerve.

On the other hand, clinical methods of testing the sensations of touch and proprioception are notoriously crude. Even if an entire thoracic nerve is divided, the sensory loss is so slight that it can be detected only in a cooperative patient by means of von Frey hairs. Likewise, if the radial or median nerve is divided, no loss of position sense in the lateral three fingers is ascertainable.

In view of these facts, I doubt whether one is warranted in drawing conclusions as to the size of fiber involved when the tendon reflexes are found to be absent at a time when the only sensory modalities lost clinically are pain and temperature sensibility.

DR. D. DENNY-BROWN: I do not mean block of conduction tracts in the cord; I refer to block of reflex function and pain sense at the synapse. It is necessary to prove that a zone of segments of gray matter is not first affected. Gasser's criteria differed from those used in this investigation. In the present instance, a reflex is pitted against sensation. The reflex is a more delicate phenomenon. If reflexes are abolished early and sensation is present late, the difference certainly has meaning; but it is easy to inhibit reflexes without disturbing sensation. It is common for reflexes to be impaired in diseases such as polyneuritis without demonstrable loss of sensation. One assumes that a reflex is a sensitive indicator but not that reflex function, or even the specific reflex function, is impossible in those circumstances. It is common knowledge that after hemiplegia in a paretic patient with absence of the ankle reflex, the ankle reflex returns. The ankle reflex is quantitatively diminished, but if reflex excitability rises it will return. It is a quantitative sign. It seems to me that the difficulty raised by this interesting observation could be resolved experimentally. In a spinal preparation, stimulation of the dorsal columns causes movement of the hindlimbs. Impulses pass antidromically into the proprioceptive system. Such a response could be tested before and after the introduction of anesthetic into the subarachnoid space and any differential effect on the response and on the tendon reflex compared. A simpler method would be to infiltrate an area around the sciatic nerve in man with the same anesthetic and see whether pain is abolished at the same time as the ankle reflex.

DR. STANLEY J. SARNOFF: We are most grateful for the stimulating and provocative comments made by Drs. Denny-Brown, Yakovlev, Schwab, Poppen and Sweet.

In reply to Dr. Schwab: I had not read Jacobson's work. It would seem, however, that the sequence of events as we see it is sufficiently rapid to cast doubt

on spontaneous or induced relaxation as an adequate explanation for the loss of the tendon reflexes. In cases in which the differential spinal block sets in early, owing to a larger initial dose, the tendon reflexes may disappear in from five to eight minutes, during which the patient may be shifting around on the table, and is anything but relaxed. Indeed, he may be somewhat apprehensive at that time.

Dr. Yakovlev's suggestion is provocative. The idea of preferentially depressing the reactivity of the anterior horn cell indirectly by blocking certain of the sensory modalities in the afferent roots had not occurred to us.

We are particularly grateful to Dr. Denny-Brown for his penetrating observations. The question of the site of action of the procaine in spinal anesthesia is certainly an important one and, curiously, has received little attention. There are, however, pertinent observations in the literature on peripheral nerve block and spinal block that would seem to confirm our impression that the interruption of the nerve impulse occurs at the nerve rootlet rather than within the spinal cord proper.

The first of these is work by Kirschner in Züringen (Spinal Zone Anaesthesia Placed at Will and Dosage Individually Graded, *Surg., Gynec. & Obst.* **55**:317 [Sept.] 1932). He worked out a method of what he called zonular spinal anesthesia. This consisted in withdrawing large amounts of spinal fluid and replacing them with air so that the upper level of the spinal fluid was in the region of the dermatome segments he wished to anesthetize, for example, the ninth thoracic segment. With the patient in the 20 degree head-up position, an anesthetic agent is introduced which is not miscible with, and is lighter than, the spinal fluid. It rises to the upper level of the spinal fluid and produces anesthesia of the few dermatome segments with which it is in contact. Above and below this band of anesthesia, sensation and motor power are unaffected. If the anesthetic works on the axon within the cord, sensation and motor power below the area of contact should be abolished. This does not occur. If it works on the synapse proper, even so, a certain proportion of afferent impulses (those which occur in the area under the influence of the agent) should be interrupted. Even this does not occur. These observations have been extensively confirmed by Phillipides.

Second, Henibecker, Bishop and O'Leary examined the order of disappearance of nerve impulses after the induction of a spinal block and that after peripheral nerve block. They are identical in every respect. In a spinal block, if the action of the procaine were on the greater mass and complex architecture of the spinal cord itself, with its system of segregated axons, one would expect differences in the sequence of events that follow the induction of the block.

Third, Loster withdrew samples of spinal fluid from various levels in the human subject at serial intervals after the introduction of 150 mg. in 3 cc. of cerebrospinal fluid, i. e., a 5 per cent solution at the third lumbar segment. Analysis of these samples revealed that, roughly paralleling the period of anesthesia, the spinal fluid contained concentrations of procaine which are known, from laboratory investigations, to be capable of interrupting the nerve impulse at the axon. From this observation, one is led to believe that whatever else is happening within the spinal cord, the rootlet itself is exposed to a concentration of the agent which is capable of affecting the impulses it conducts.

Fourth, it is frequently possible to produce hemianesthesia within the spinal canal. That is, a concentrated, hyperbaric solution of procaine is introduced with the patient lying on his side. He is left in that position for fifteen or twenty

minutes, and the result is an anesthesia almost exclusively of the dependent side. It seems to us that if the action were within the cord itself this would probably not occur, and that the effect is more understandable if the site of action is on the rootlet.

Dr. Poppen's experience lends support to these theoretic considerations.

Charles L. Kubik, M.D., *Presiding*

Regular Meeting, May 8, 1947

The Contrast in Incidence of Compulsion Neurosis and Psychopathic Personality in the Armed Forces: Psychiatric and Social Implications.

Dr. Joseph J. Michaels and Dr. Robert T. Porter.

Medical literature has been primarily concerned with studies of the pathologic aspects of human function, especially in the realm of psychiatry, but little has been written of the factors which enhance good adjustment or of the variations from the mean which may exist without serious disturbance of an adequate adaptation to life and its many stresses. In this study the low incidence of obsessive-compulsive neurosis is contrasted with the high incidence of psychopathic personality in the Army. The material is based on two sources: (1) a series of cases reported in the literature, of relatively unspecialized character and sufficient size, and (2) a series of 1,383 neuropsychiatric patients studied at the Newton D. Baker General Hospital over a period of one year (August 1944 through July 1945). The incidence of compulsion neurosis at the Newton D. Baker General Hospital was 0.2 per cent, with a similar low incidence (0.3 to 0.4 per cent) from the literature. In contrast, the incidence of psychopathic personalities at the Newton D. Baker General Hospital was 3.5 per cent, and that from sources in the literature was much higher (10 per cent).

The psychopathic personality, whose responses are impulsive, experiences the milieu of the armed forces as too restrictive, and he cannot adjust. The psychopathic person is notorious for his inability to bind his anxiety and tension. The obsessive and compulsive symptoms in a person with a compulsion neurosis are defense mechanisms which serve the purpose of allaying, or actually binding, anxiety. The Army and Navy, with their discipline, regimentation, reports, rules, regulations and emphasis on orderliness, cleanliness and economy, may be considered as vast compulsive organizations. The person with a compulsive character finds himself in a compulsive milieu with which his tendencies are in harmony: Reports on studies of soldiers and air crew members who successfully withstood the stress of prolonged combat duty indicated that a significant percentage exhibited compulsive character traits, and that men with "rigid personalities" or compulsive personalities generally completed their tours of duty and tended to be steady and reliable.

The premise is advanced that a degree of compulsiveness is generally essential to strength of character, and compulsive character traits are regarded within the range of normal personality variants, as distinguished from symptoms of compulsion neurosis, which are pathologic exaggerations of such variants. A certain degree of compulsiveness is considered worth while to all citizens of current civilized society, as well as to members of the military forces. Among the influences which contribute to compulsive character traits, religious training certainly war-

rants mention. The other authority capable of imparting compulsive rules of conduct is usually the parents or parent substitutes. It is suggested that early training, which instills some compulsive character traits in children by virtue of respect for authority, remains necessary in present day culture.

DISCUSSION

DR. ARTHUR F. VALENSTEIN: I am impressed by the thoroughness with which the literature has been surveyed and by the consistency in the data as presented by Dr. Michaels and by the many other authors whom he has cited. The strong measure of validity which this suggests is, moreover, supported by a related research project, of which I should like to speak briefly.

Several months ago I had the privilege of reading this stimulating paper by Dr. Michaels and Dr. Porter. Out of it, and a subsequent provocative discussion with Dr. Michaels, grew certain ideas which are now embodied in a research project currently being carried out at the Veterans Administration Mental Hygiene Clinic, Boston Regional Office. This study is already sufficiently advanced to permit the substantiation of some of the premises offered this evening.

My colleagues and I have established that there is a significant difference between the type of veteran who seeks treatment at the Mental Hygiene Clinic and the overtly neurotic soldier or sailor who was recognized in service. A comparison of neurotic soldiers, as they were clinically encountered, with neurotic veterans who come to our attention shows a significant reversal of the ratio of the incidence of compulsive neurosis to that of psychopathic personality.

A sizable group of the veterans who seek treatment at the Mental Hygiene Clinic successfully completed a full tour of military service, sometimes including sustained combat duty, and most of this group returned to civilian life as point dischargees, having required little or no psychiatric recognition or treatment at any time during their period of service. Among the patients I have treated was a fighter pilot who shot down seven German planes and went through an arduous year in a German prison camp prior to liberation. Currently, I am treating another veteran who went through nine months of infantry combat as a squad leader and who was awarded the Silver Star. He is now being considered for the Distinguished Service Cross. A third man, a bombardier, completed an extremely severe tour of duty with the Eighth Army Air Force, during which all his crew mates were either wounded or killed. None of these men became psychiatric casualties while in service, but all of them now require psychotherapy for lasting manifestations of anxiety, which include irritability and episodic periods of mild depression, attributable to reality combat stresses in conjunction with their basic character difficulties. Such patients as these have been seen by all the psychiatrists who participate in the treatment program of the clinic.

The outstanding trait in the personality of these 3 patients, and of others like them, was their intense drive to succeed, their excessive meticulousness and their rigid perfectionism, by means of which they try to protect themselves against anxiety related to their fundamental feelings of inadequacy and helplessness. They are persons whose character formation is largely colored by compulsive mechanisms.

In contrast to this group, we see relatively few psychopathic personalities; this differs sharply from our experience in the service. In the setting of civilian life, psychopathic persons, in contrast to persons with the compulsion type of person-

ality, show little inclination to seek or to accept psychotherapy. Furthermore, our study, in so far as it is completed, confirms the usefulness of the concept which designates the compulsion neurosis and the psychopathic personality as the opposite poles of a spectrum which delineates ego strength (compulsivity) at one extreme and ego weakness (impulsivity) at the opposite extreme.

DR. HERBERT I. HARRIS, Portsmouth, R. I.: My fancy is caught by Dr. Michaels' reference to the psychopathic patient's lack of ability to inhibit response to a stimulus. The impulsive behavior which results from this lack is common to both the child and the savage, who, like the Australian bushman, lives in a loose social group deficient in taboos.

Inhibitory activity ranges in complexity from the arrest of the heart beat by stimulation of the peripheral end of the vagus nerve to the prolonged inhibitory activity characteristic of the obsessive-compulsive personality.

How can we explain the psychopathic personality and the obsessive-compulsive neurosis? The normal child acquires simple inhibitory traits through repeated trial and error and doubtless thereby prepares the ground for the more complex inhibitions that he must learn. The latter develop through the age-old disciplines, denials and urgings given him by those he loves—his parents and siblings, and later by all his associates. At first these inhibitions are external—they come from those about him—but memory and the need of love from his parents cause these prohibitions and urgings to be retained in his mind, where, by some form of neural accretion, they become organized into a correlated and dynamic whole, whose outward expression is that in the speech and acts of the person which one calls conscience or superego. In the obsessive-compulsive neurosis the conscience appears to be most highly developed. In the primitive savage, in contrast, whose impulsive nature is often assumed as a matter of course, one may observe a different process. Either because of qualitative neural limitations or because of a different child-parent relationship, the savage develops a less powerful inner conscience. His conscience is external and is composed of the multitude of fear-invested taboos that control nearly every waking act. Removed from the threat of these external conscience symbols, the savage might well behave like the impulsive psychopathic personality.

Between these two, the child and the savage, stands the psychopathic personality—neither fish, flesh nor good red herring. What may one assume to be the cause or causes of the development of the psychopathic personality? One has two choices: the organic, according to which one assumes that the psychopathic patient has a defective nervous system, caused perhaps by a cosmic ray bouncing off him as he vegetated in bipartite seclusion as sperm or ovum, and the environmental, according to which one assumes that he failed for various reasons to love his parents and so absorb the mild and harsh admonishments and urgings which they gave him during his developmental years. Those among you who are sanguine and believe that psychiatry is making progress cannot but choose the latter view. If you have not read August Eichorn's "Wayward Youth," I urge you to do so.

To end on a somewhat less brow-furrowing note, I should like to point out that one is here faced with a difficult matter of judgment. Dr. Michaels points out that the patient with the obsessive-compulsive neurosis, who possesses conscience *par excellence*, makes a good man in combat, whereas another writer said some time ago, "Thus conscience does make cowards of us all." Perhaps Dr. Michaels would like to come to his own defense in this disagreement with the great poet-psychiatrist.

Peripheral Nerve Injuries in Great Britain During World War II: A Review. PROF. HERBERT J. SEDDON, Oxford, England.

One of the first problems calling for solution was a working classification of nerve injuries that was sound pathologically. An analysis based on the first 500 cases dealt with at the Oxford Centre suggested that it was possible to regard most nerve injuries as being due to one or more of three types of damage.

Neurotmesis.—In this condition the nerve is completely disorganized, although it may appear to be in continuity. All essential elements are interrupted, and there is complete degeneration distal to the lesion. The term is more precise than division in that it includes conditions such as severe traction injuries and nerve damage due to injections of sulfanilamide—lesions in which the nerve may be completely blocked by intraneural scar tissue. The only effective treatment is resection and suture.

Axonotmesis.—In this condition, which can readily be studied experimentally, the axons and their sheaths are completely interrupted, but the internal architecture of the nerve is preserved, in particular, the endoneurial tubes. There is complete peripheral degeneration; but regeneration is spontaneous, and the quality of recovery is good, since the outgrowing fibers remain in the tubes to which they belong. Thus, restoration of independent movements and of accurate tactile localization may be confidently expected.

Neurapraxia.—The axons remain in continuity, but the myelin sheaths, especially those of the larger fibers, are interrupted. There is dissociated paralysis, which is predominantly motor, but at no time is there a reaction of denervation in the affected muscles. Recovery is rapid and complete; it may occur simultaneously throughout the whole zone of disturbance.

Many nerve lesions are due to mixtures of the three types of damage, and analysis of these mixed lesions presents a difficult neurologic problem.

A major difficulty is to distinguish between neurotmesis and axonotmesis, since at first the clinical picture is identical. It has been found that open wounds cause neurotmesis in about 1 of 2 cases; as a matter of policy, it is therefore desirable to explore all nerve lesions due to open wounds as soon as possible after healing of the primary wound. On the other hand, closed nerve injuries, in which the nerve has been damaged by a fracture, are found to be an axonotmesis in about 4 of every 5 cases. Hence, it is justifiable to delay exploration until it is evident that spontaneous regeneration is overdue. Estimates of the rate of regeneration based on the rate of recovery of motor function show that the initial rate is considerable, perhaps 3 mm. a day, the regeneration then slowing to 1 or 1.5 mm. a day and proceeding even more slowly in the final stages. The rate is represented by a curve rather than by a straight line. However, for practical purposes, it is still safe to regard as basic as an over-all rate of 1 mm. a day. If, for example, the radial nerve is injured by a closed fracture at a point 10 cm. above the elbow joint, one would expect signs of recovery in the brachioradialis muscle about one hundred days after injury, the point of entry of the motor branch into the brachioradialis being just proximal to the elbow joint. Absence of recovery after such a period would be an indication for exploration. Electromyography is of value; in a case of axonotmesis motor units will be detected in a muscle several weeks in advance of the return of voluntary power.

Hitherto, primary suture has been regarded as the treatment of choice when the nerve is divided by a clean incision. However, comparison of the results of

primary suture with those of early secondary suture, and the examination of material obtained at secondary resection and suture of nerves dealt with by primary suture, indicate that the delayed operation is preferable. At the time of the primary operation it is impossible to make a sure estimate of the extent of intraneural damage on each side of the line of division. Thus, one may find that after a primary suture regeneration is hindered or completely prevented by intraneural collagenization. If a secondary operation is carried out three or four weeks after the initial injury, the extent of this intraneural damage is easily detected on resection of the nerve ends. The state of the nerve sheath is also of importance. The sheath may be split or frayed by the initial injury and will then be in a most unsuitable state for suture. After three or four weeks, small tears will have healed, and the sheath will have hypertrophied to perhaps three times its normal thickness and will then hold sutures well. No nerve suture can be regarded as satisfactory unless there has been adequate mobilization of the central and peripheral stumps. It is rarely justifiable to expose the stumps widely at the time when the original wound is repaired, but a generous incision may be made with impunity within a few weeks of healing of the primary wound. The conclusion is that, although a good result can often be obtained by primary suture, the result cannot be guaranteed, whereas a successful result may be confidently predicted after a well executed secondary operation. Nothing should be done to the nerve, except to bring the ends together, at the time when the primary suture of the skin is performed.

The most serious technical problem in peripheral nerve surgery is that presented by the large gap. It is possible to close gaps up to 17 cm. by mobilization of the nerve stumps and suture with the neighboring joint or joints in a position of acute flexion. Unfortunately, the subsequent straightening of the limb, however carefully carried out, frequently inflicts a traction injury on the nerve which may be even more serious than the original damage. Thus the biologic limit of application of the standard method of nerve repair is stricter than the anatomic. In general, flexion of the elbow or knee beyond a right angle is unjustifiable. When the gap is large, successful suture may sometimes be achieved by means of preliminary bulb suture and, rarely, by bone shortening. But the only generally satisfactory solution is to close large gaps by some kind of nerve graft.

Homogenous grafts have been uniformly unsuccessful. It is probable that the implantation of foreign material produces an acquired immune reaction, similar to that induced by homogenous skin grafts, and it is unlikely that any progress will be made in this direction until some means has been found of "denaturing" homogenous grafts. At present the only hope lies in autogenous grafting, with its obvious intrinsic limitations. At the Oxford Centre, autogenous grafts have been employed in 58 cases, and in over one half of them the restoration of function has been as satisfactory as 'that seen after the most satisfactory suture of the same nerve at the same level. Single strands of cutaneous nerve may be employed for the repair of digital nerve defects; cables consisting of two to four strands may be used for larger nerves, and in a number of cases in which there was extensive damage to two major nerves a segment from the less important nerve was used for repair of the more important one. Although these large free grafts show histologic abnormalities, they often provide satisfactory channels for the conduct of fibers from the central to the peripheral stump. The radial and ulnar nerves have been employed with success; but it appears that the lateral

popliteal nerve (two segments of which have been used to bridge a gap in the medial popliteal component of the sciatic nerve) is too large to survive, and some form of nerve pedicle grafting seems necessary in order to maintain the blood supply of the transplanted tissue. All grafts shrink, and it is wise, therefore, to make the implanted segment rather longer than the gap that has to be bridged. Since the nutrition of a free graft is at best precarious during the days immediately following implantation, care should be taken to place the graft in a well vascularized bed. If scarring is extensive, the graft should be led through a by-pass around the main zone of damage. Since it has been shown that nerve grafting is a reasonably reliable procedure, there is much to be said for employing a graft for repair of a partially divided nerve, the graft being inlaid into the defect. This operation has been employed in 5 cases, with encouraging results.

Results of Nerve Suture at Five Nerve Injury Centers in Great Britain.
MR. B. B. ZACHARY, Oxford, England.

Mr. Zachary described the method of assessment of end results: For the radial nerve, for example, M_1 indicates a little return of power in the proximal muscles; M_x, some return of power in the distal, as well as in the proximal, muscles; M_3, recovery in almost all muscles, so that they are capable of contraction against gravity; M_4, some restoration of independent movement, and M_5, perfect function. Restoration to perfect function had never been seen after nerve suture; for statistical purposes, grade M_3 was regarded as a satisfactory criterion. The results were collected on the basis of the total number of cases in which recovery reached the grade M_3 (a comparable sensory recovery) at intervals of six, twelve, eighteen, and so on, months after suture; as would be expected, the time required before recovery of grade M_3 was achieved in a given number of cases was shorter when the level of suture was in the peripheral part of a limb. Three factors were found to be of prognostic importance: the level of the suture, the interval between injury and repair of the nerve and the extent of resection. In the radial nerve, the level of suture seemed to be an immaterial factor in results, but it was significant in the results for the ulnar nerve. There was a significant fall in the proportion of good results when the delay between injury and repair was greater than six months. There was also a smaller proportion of satisfactory recoveries when the length of resection exceeded 5 cm.

DISCUSSION

R. B. ZACHARY, Oxford, England: In Great Britain the follow-up observation of nerve injuries has been carried out mainly by the five peripheral nerve injury centers sponsored by the Medical Research Council. It was realized that the final assessment of the results of nerve suture could not be made just yet, but an interim analysis was undertaken for the purpose of finding the most satisfactory method of collecting and arranging the data and of making the final analysis.

The first requisite is to have adequate data concerning the actual nerve repair and a standard method of estimating recovery. The assessment of recovery must have a neurologic basis; it must be as objective an estimate as possible of the strength of the recovering muscles and of the extent and quality of the returning sensibility. If the assessment is made on a primarily functional basis, e. g., the usefulness of the injured limb, many other factors, such as the condition of joints and tendons and the adaptability of the patient to his disability, come into play and obscure the significance of recovery due to reinnervation.

An important point arises in connection with the time at which recovery is assessed. If the most recent examinations of the patients are the ones used in the analysis, the figures will include some assessments made at one year and others at two, three, four or five years and at intermediate periods. Any difference between two groups of cases might, therefore, be due in part to unequal follow-up periods in the two groups. To eliminate this variable factor, the assessments used in the analysis are those made at twelve, eighteen and twenty-four months, and so on, and the same follow-up period can be used for two groups to be compared.

Motor and sensory recovery must be analyzed separately for each nerve, and one can then take a certain grade of recovery and consider the percentages of sutures reaching this grade under various conditions. For example, M_3 is that grade of motor recovery in which all important muscles are acting against gravity and resistance. In the case of the radial nerve this grade of recovery is a useful one, and, with this criterion, one can consider the influence on recovery of (1) the site of suture, (2) the delay before suture and (3) the length of resection.

If one finds a difference between the results of high and low sutures—a difference which is statistically significant and is in favor of the low sutures—one cannot assume that a high site of suture is an adverse factor, because a high site of suture is more frequently associated with a long delay or a long resection than is a low site of suture, and it might be the delay or the length of resection which is the main controlling factor. Similarly, those sutures performed after long delay often require long resections, and thus, in order to decide which factors are in themselves adverse, one must eliminate the other variables. For example, the influence of delay before suture is assessed by considering only low sutures with resections of less than 5 cm., thus eliminating high suture and long resections.

An analysis which does not take account of these variable factors must give an incomplete view of the situation, data which may mislead rather than help; yet, to provide figures which in the ultimate analysis have a statistical significance, large numbers of sutures are necessary—sutures performed under known conditions and assessed by a standard method. It is hoped that the present schemes for follow-up examination both in this country and in Great Britain will provide such data.

DR. JAMES C. WHITE: A few months before Pearl Harbor I visited Mr. Seddon's clinic, and I was impressed then, and during his paper tonight, by the degree of thought that he and his associates were putting into this problem of nerve injuries, not only the clinicians at the Wingfield-Morris center for nerve injuries, but also the anatomists and physiologists of Oxford University. I was, in fact, more impressed by the degree of finesse being put into this work than by that of any other clinic I have visited since. If one reads the recent comments of the older surgeons who worked on this problem in World War I in this country, one will often see the statement that nothing new has been discovered that they did not know about in World War I. It seems to me that the significant point brought out by Mr. Seddon and in the writings of Barnes Woodhall is the importance of making an early exploration in all cases of nerve injury. It is impossible to distinguish clinically between Mr. Seddon's terms neurotmesis and axonotmesis. In cases of the former, in which the nerve trunk has been severed, suture after nine months, a delay which was usual in World War I, never gives as good results as early suture.

You may be interested to hear about the follow-up project of the Sub-Committee on Nerve Injuries of the National Research Council. We of that committee have completed careful plans to review 7,000 cases in the Army nerve suture registry and some 1,000 cases of similar injuries in veterans of the Naval and Marine Corps. It is hoped that funds will soon be available to set up five centers for the study of these cases. One is to be located at the Cushing and Massachusetts General Hospitals. Our group is trying to formulate accurate standards of motor and sensory recovery, skin resistance as a measure of autonomic regeneration and electrical tests of nerve conduction. If the program goes through, we shall, for the first time, have accurate information on nerve recovery in a large and well controlled series of cases, and thus be in a position to avoid a repetition of the unfortunate experience of World War I, in which all such valuable information was lost because the late results were never reviewed.

DR. D. DENNY-BROWN: Mr. Seddon's account of his experience with nerve suture was of special interest to me, since I was fortunate to see the beginnings of his unit for nerve injuries at the Wingfield-Morris Hospital, near Oxford. The excellent work which has come from that hospital is well known. The end results, after careful classification and follow-up confirmation, show a most remarkable degree of success in dealing with a difficult problem.

I was interested to hear Mr. Seddon stress the importance of vascular supply of grafts, for in the beginning there was a tendency to overlook this point. The basic difficulty in the question of grafts is the peculiar habits of a cell which is commonly called the Schwann cell but which I think is a fibroblast with ability to deposit collagen. Dense collagen may ultimately block all chance of recovery, as Mr. Seddon has shown in human material. More study of the habits of this cell and the factors which induce it to produce collagen will be well worth while. Ischemia is certainly one factor. Another is the length of time these cells are left without relation to a nerve fiber; the longer they lie in a degenerating nerve, the more they appear to change their character. Changes in the most proximal portion of the peripheral stump probably result from the ischemia incident to the original trauma. I should like to ask Mr. Seddon whether it would not be practical to leave excision of the peripheral stump until later, making the first junction proximal and allowing the nerve fibers to grow into the graft and at a later date excising a portion of the peripheral end of the graft and the proximal end of the peripheral stump and making a suture at that level. The growth at that level would then start at a region of nerve without a great increase of collagen. Mr. Seddon feels that the peripheral junction often looks better than the proximal, but I would still maintain that, as viewed in cross section, these tubes had already become much too narrow to permit optimum development of fibers.

DR. HENRY C. MARBLE: At the Massachusetts General Hospital, most of the nerve injuries are of the upper extremities, that is, about the hand, wrist and forearm. Furthermore, they are often part of extensive lacerations of muscles, tendons, fascia and bones.

Patients with such injuries are admitted to the emergency ward and are cared for by the general surgical service. It thus appears that the vast majority of nerve sutures in that hospital are performed by the general surgeon. I urge that the surgeons make prompt, accurate neurologic diagnosis, a careful and complete diagnosis of the injury to tendon, muscle and bone, and that he carry out such procedures as are necessary to repair these injuries. So far as the nerves are

concerned, our experience with delayed nerve sutures is nil. We have always urged that in nerve sutures one should repair only the neurilemma, making careful, exact closure of this sheath. Dr. Edward Hamlin has collected and studied the end results of our cases over a period of seventeen years. He will report his results. They are very satisfactory. We have had return of sensation after primary nerve suture in better than 85 per cent of cases. In secondary suture the results are fully as satisfactory, but the problem of retraction of the proximal part of the nerve makes the operation more difficult and the whole procedure unnecessarily complicated. We feel sure that when freshly cut nerves are sutured, and honestly sutured, the sensory return should be very nearly perfect. With respect to great gaps between the nerves, such as are seen in war injuries and following major automobile accidents, we have had recently a most interesting experience. In 4 cases I did a nerve graft. In each case a cable made up of three or four strands of the sural nerve was used. In 1 of these cases a gap of 7 inches (17.5 cm.) was closed with three strands of sural nerve. On a recent examination it was clear that the patient had sensory return. We were able definitely to determine that the man had return of sensation over the area formerly supplied by the median nerve. Needless to say, these are subjects that should come in for a great deal of thought and study during the coming years.

I am very glad to have listened to Professor Seddon's experience. He did an interesting, important and necessary study.

My only admonition to a group of neurologists is that they so teach their students that they will recognize injuries to the nerves in the emergency wards, in order that those nerves may receive prompt and adequate care. I urge that they teach young surgeons so that they may either immediately after, or delayed as Prof. Seddon says, meticulously suture those nerves together, so that the patient may have the best opportunity for a good functional result.

Dr. Edward Hamlin: My experience is slight as compared with Mr. Seddon's. Of some interest is the observation that the early and immediate sutures do as well as the delayed. It might be added that the very much delayed sutures also appear to do as well. Some of our best results have been in the plus two, plus three and plus four year periods. I was interested in Mr. Zachary's discussion of the determination of the end result. Our criteria for an end result are not as exacting as his. Before one presents any sort of figures on the result of nerve suture, one must make many apologies and many definitions, which I shall not bore you with. A good result, we said, was a useful hand—one with no anesthesia, with ability to put on clothes and perform ordinary functions—and there we let it go. Our statistics concern some 242 nerves of the upper extremity. There were good end results in 85 per cent. The most interesting feature was that good results were obtained for the ulnar nerve in some 95 per cent of sutures. The good results for the radial nerve were far below par, in only 46 per cent of cases.

Dr. Joseph Barr: Injuries to the radial nerve, no matter how or where treated, give poor functional results in a considerable percentage of cases, and it may take as long as two years to produce an M_3 result. That is particularly true in the case of war injuries, which are worse than civilian ones. High explosives produce severe damage up and down the nerve trunk. The results of nerve surgery are not satisfactory in most cases of such laceration. With tendon transplantation, however, the results are very satisfactory in a high percentage

of cases. It is so satisfactory that Sir R. Jones said that in cases of injury of the radial nerve he would prefer to do a transplantation immediately and get a functional result in three months, rather than do a suture which would produce a doubtful result in two years. One can get good functional results by tendon transplantation, not only in cases of injury to the radial nerve but also in cases of irreparable damage to other peripheral nerves. In every instance in which there is loss of function due to irreparable nerve damage the case should be carefully studied by a competent orthopedic surgeon to determine whether function can be improved by such procedures as tendon transplantation and stabilization.

DR. ARTHUR L. WATKINS: What would Mr. Seddon think were the important features of after-care? He mentioned electrical stimulation as probably helpful in preserving muscles or preventing progressive changes. What does he think about rigid immobilization, or about allowing some motion, or does he think that free motion within small range is detrimental? Can anything be done to prevent progressive changes in the nerve during the period of delay before regeneration takes place—the changes he demonstrated in his slides?

PROF. HERBERT J. SEDDON: I am a little frightened because I tried to keep the field narrow and it has widened. We could go on all night.

As to the policy of exploration, we advocate it early, whenever there is a wound.

As to Dr. Denny-Brown's question about the Schwann cells, I hoped that he would not mention it. I have read his paper, and we have discussed it furiously, about whether repair of nerve is brought about by a Schwann cell or a fibroblast —I am not sure. I am not a histologist, but I shall talk to him in private about it. There is something in what he says about joining the proximal stump. Dr. White has already done this in patients we saw this morning and in a patient on whom I operated three weeks ago. Dr. Denny-Brown would agree that it would make no difference in the posterior stump itself.

I was grateful to Dr. Marble, for he emphasized the practical and important points in the field of general surgery, that is, that these injuries do occur in peacetime and do require a great deal of attention, especially on the part of the house officers who first see these cases. I still think that early secondary suture is better than primary.

With regard to grafting, there are three men to whom we owe a great debt—Ballance, Duel and Balin. Dr. Hamlin spoke of end results. I find it at variance with my experience when he says that he has not seen any significant result from delay in repairing a nerve. It is not my experience at all. I am glad if it is true, for I shall feel encouraged to suture nerves that have been divided two or three years, when I should have said that it was not worth attempting.

As to suture of the radial nerve: In good transplantations of radial nerves, the results are variable. Our aim is to study not our successes but our failures. We divide them into two groups: inevitable failures, because of the extent of damage, and failures that would be put right by technical advances. Perhaps I can say that in 8 of 10 cases I can promise good results from suture, and that in the other 2 cases suture would not be worth while.

My associates and I have done a good deal of work on electrical stimulation. Galvanic stimulation does maintain muscle, but it does not bring it back to its former state. One of the most terrible things has been mobilization of hands. If they are not splinted right, they should not be splinted at all. Movement of

paralyzed muscle is harmful. Moving a muscle through its range of movement causes no harm at all. There is a place for splinting, but the patient must be able to move in his splint.

Charles L. Kubik, M.D., *Presiding*

Regular Meeting, Oct. 16, 1947

Focal Epilepsy: Statistical Study of Its Causes and the Results of Surgical Treatment. I. Epilepsy Secondary to Intracranial Tumors; II. Epilepsy Secondary to Cerebral Trauma and Infection. DR. JAMES C. WHITE, DR. W. JASON MIXTER and DR. C. T. LIU.

This paper was published in full in the *New England Journal of Medicine* (**238**: 89 [June 24]; **239**: 1 [July 1] 1948).

Sociopsychologic Structure of the SS: Psychiatric Report of the Nurnberg Trials for War Crimes. DR. LEO ALEXANDER.

This paper was published in the May 1948 issue of the ARCHIVES, page 622.

DISCUSSION

DR. TALCOTT PARSONS: I found Dr. Alexander's paper most interesting and stimulating, and also rather overwhelming in the magnitude and complexity of the problems which it raises. I say that from my own point of view, that of a sociologist. Unfortunately, I am not familiar with the current accumulation of material on Germany which has become available since the Allied authorities got in there, and which has enabled Americans to examine many of the things which had been discussed and speculated about by psychologists and social scientists under the impact of the war and what had gone with it. In the few minutes available, I can comment only on the problem that is raised by the latter part of Dr. Alexander's paper. I am one of the social scientists who have been most impressed by and interested in the contributions which psychiatrists and psychologists have been making in extending our range of interest, as Dr. Alexander said, from the close-up study of the individual to attempts to analyze in the same or similar terms the implications of findings on that level to the behavior of large groups and social systems. I agree with him that important contributions have already been made in that direction and that more are to be expected. At the same time, I think the problems are exceedingly complex and that the solution must be sought on several different levels. What are Germans as typical individuals like? How did they get to be Germans in that sense? What implications are there in the fact that they are the kind of people they have been for their behavior under various circumstances in the mass? I am convinced that there is no simple solution to these problems. There is a good deal of evidence that the German social system as it existed in the period in which the Nazi movement took hold was in certain fundamental respects unstable. But it seemed, I think, to most Europeans before World War I to be particularly stable. Hindsight and the resources of social science and psychology have given considerable insight into some of the rifts that existed then. I should like to suggest one particularly important point that I do not think has been sufficiently emphasized. This apparently stable social order which was conspicuous in Imperial Germany seems to

have been taken by the German people emotionally in a peculiar way, peculiar from our point of view, in that there was a certain dissociation between the established social order and its system of status, on the one hand, and people's most private aspirations and emotional involvements, on the other. There was a peculiar formalism about the social order and about attitudes towards status within it. Such status was something very important to have and to be secure about, and yet something that in another, affectively more fundamental, sense did not really matter very much. The genesis of that sort of dissociation is a very complex problem which, among other things, involves the social and religious history of Germany. However, I think that it, along with more specific and temporary social strains, was crucially important in setting the stage for the large scale movement of what one might call the emotional explosion known as Naziism. This peculiarly German phenomenon could not have stood alone, for, as in every complex society of the Western type, there was a vast amount of underlying emotional tension. Whether it was greater in Germany than in other Western countries, I doubt that anybody can judge. But since its sources in the social structure were in certain respects distinctive, it was channeled more definitely in certain directions in Germany, and further distinctive features were derived from the contemporary social situation. Once channeled that way, there was the material for mobilization on the mass scale of aggressiveness and destructiveness which characterized the German nation in its Nazi phase. One aspect of the consequence was the unparalleled movement of nationalistic aggressiveness, but another made possible the development of an elite Nazi group within Germany according to the pattern Dr. Alexander described this evening. A more drastic break away from the established values of civilized social life in the Western world is probably not to be found anywhere. In attempting to understand what large scale social processes have been involved in this phenomenon, one must work out some complicated interactions between these larger aspects of social structure and the movements of social change which certainly are not simple psychologic phenomena in the ordinary sense, although they involve a complex interplay with psychologic aspects. On the other hand, the psychologists should be able to tell much about the way in which the conditions produced by the Nazi movement create such motivational structures as Dr. Alexander described, and what instabilities and potentialities are involved in them. I have not elsewhere heard such a graphic and penetrating account of how within the SS organization the extreme of the psychologic pattern of destructiveness was worked out. It was a most interesting, if terrifying, account.

PHILADELPHIA NEUROLOGICAL SOCIETY

Anthony S. Tornay, M.D., *Presiding*

Regular Meeting, Nov. 28, 1947

Mucormycosis of the Central Nervous System: Report of a Case. DR. WINSLOW P. STRATEMEIER, Wichita, Kan. (by invitation).

Infection of the human nervous system with fungi is uncommon. In 17,400 autopsies at the Johns Hopkins Hospital only 10 cases were reported. At the Philadelphia General Hospital, only 4 cases were reported during the past twenty years. Infection of the human nervous system with fungi of the Mucor group is

extremely rare. Only 5 cases have been reported in the literature. The mucors belong to the mold fungi and the class Phycomycetes. Lesions have been observed in man and in animals and consist of granulomatous accumulations in the various organs. The majority of lesions have occurred in the lung and skin. The central nervous system is least often involved.

In 1885 Paltauf described the only known case of involvement of the central nervous system by the Mucor fungi. Gregory and associates (*Bull. Johns Hopkins Hosp.* **73**:405, 1943) described the first 3 cases in which there was direct involvement of the central nervous system via the paranasal sinuses and the eye. A fourth case was reported by LeCompte and Meissner (*Am. J. Path.* **23**:673, 1947). The 4 patients all had severe diabetic acidosis with proptosis of one eye on admission.

The following case is presented because of its similarity to the 4 cases just cited and because it is apparently the sixth case reported of mucormycosis of the central nervous system.

A Negro woman aged 32, obese, was admitted to the Philadelphia General Hospital on Sept. 4, 1944 in diabetic coma following a heavy alcoholic bout. There was an inadequate history of dyspnea, vomiting and loss of consciousness. The breath had a strong odor of acetone, and Kussmaul respiration was present. The left eyelid was swollen and ptosed. The spinal fluid contained 28 cells per cubic millimeter and was sterile on culture. The urine gave a 3 plus reaction for acetone and sugar. The blood sugar was 400 mg. per hundred cubic centimeters, and the carbon dioxide content was 10 volumes per cent. Treatment was of no avail; pneumonia developed in the upper lobe of the left lung, and the patient died on September 6. Autopsy showed chronic empyema of the anterior ethmoid cells. The left posterior naris showed a thickened, necrotic and hemorrhagic membrane. The left turbinate bone and septum appeared to be necrotic. Unfortunately, culture of the fungi was not taken. Exact identification of the fungus is impossible in the absence of a fungous culture. Grossly, the brain showed thrombosed vessels and infarction on the orbital surface of the frontal lobes. Microscopic examination revealed ischemic necrosis, varying from cellular degeneration to complete tissue breakdown of the orbital surface of the frontal lobes. In the subarachnoid space over this area the vessels were blocked by masses of leukocytes and fibrin. In their lumens were large hyphae, with numerous branches and absence of septa at the branching points. These fungi extended around the vessels in the media and sometimes broke through into the adventitia. The involvement was strictly localized. The mucosa of the middle turbinate on the left side was deeply infiltrated with lymphocytes and occasional fungi and spores. The fungus had apparently spread from the naris to the brain. There was mild outpouring of lymphocytes in the subarachnoid space over the entire brain.

DISCUSSION

DR. HELENA RIGGS: It is of interest that all these patients were diabetic and that the infection of the central nervous system arose from an infection in the eye, suggesting, as Dr. Stratemeier has said, that the original infection is in the nose, probably with a saprophyte, and that invasion occurs when the patient goes into diabetic coma.

The possibility that these fungi were simply contaminants is not tenable. We found no other parts of the brain except over this area of necrosis in which the fungi were present; therefore, they were not a postmortem contaminant.

Multiple Sclerosis: A Review of 53 Cases with Autopsy. Dr. Thomas G. Potterfield (by invitation) and Dr. Charles Rupp.

The clinical and autopsy findings in a series of 53 cases of multiple sclerosis were studied. Thirty-three patients were women and 20 were men. The ratio of white to Negro patients was 8:1. The onset of symptoms was most frequently between the ages of 26 and 40, but occurred as early as the seventeenth year and as late as the fifty-eighth year. In approximately one-half the cases the duration of the disease from onset to death was from nine to fourteen years. The severity of symptoms did not usually necessitate the patient's hospitalization until from three to five years after onset.

The onset was abrupt in 11 cases and gradual in 42 cases. The commonest symptoms included motor weakness of one or both legs, visual disturbances, paresthesias, urinary disturbances and, less frequently, hemiplegia and speech disturbances. During the course of the illness the commonest sign was motor weakness with spasticity, which was found in all cases. Other frequent signs and symptoms included the Babinski reflex, in 53 cases; urinary disturbances, in 34 cases; sensory changes, in 28 cases; paresthesias, in 7 cases; intention tremor, in 27 cases; absence of abdominal reflexes, in 24 cases; scanning speech, in 24 cases; visual disturbances, in 23 cases; spastic paraplegia, in 22 cases; bulbar signs other than scanning speech, in 19 cases; mental symptoms, in 14 cases; pupillary disturbances, in 13 cases; fecal incontinence, in 13 cases; constant tremors, in 13 cases; Charcot's triad, in 12 cases; extraocular palsies, in 4 cases; hemiplegia or hemiparesis, in 4 cases; athetotic or dystonic movements, in 4 cases; transient peripheral nerve palsies, in 3 cases; convulsions, in 3 cases; brachial diplegia, in 3 cases, and torticollis, in 1 case.

Subjective sensory disturbances were usually referred to the extremities but were rarely limited to the face. Objective sensory changes most frequently involved the posterior columns. Signs indicative of a transverse lesion of the cord were present in 22 cases, with motor signs predominating. Mental symptoms were chiefly those of deterioration or pathologic emotionality. In 2 cases there was an acute psychosis. Of the 3 cases with involvement of peripheral nerves, foot drop was present in 2 and ulnar palsy in 1.

A history of trauma to the nervous system was obtained in 6 cases, but in 3 the association appeared to be chiefly coincidental. In 4 cases the onset of symptoms occurred during pregnancy. In 21 cases there were complete remissions; partial remissions occurred in others. Abnormalities were noted in the colloidal gold curves in 22 of the 25 cases for which data were available. These took the form of either first zone or midzone changes.

DISCUSSION

Dr. Helena Riggs: It is of interest that, despite the variability of signs, the clinicians made the correct diagnosis in all these cases which came from the neurologic wards. In only 2 cases was the diagnosis not made clinically. In 1 of these the surgeons had tried over a period of fifteen years to straighten the patient's legs, and multiple sclerosis was not suspected. She had an early stage of the disease and presented few symptoms other than paraplegia. The other case was surgical; the patient had a very acute abdominal condition on admission. The surgeons were so concerned with this that they failed to observe any of the other symptoms.

One other case might be of interest. The patient, aged 69, and apparently not disabled, was admitted for acute strangulated hernia. Simply because it was a coroner's case, I removed the brain and found most advanced multiple sclerosis. That is the oddest case I ever encountered at autopsy.

DR. GABRIEL A. SCHWARZ: In the teaching of multiple sclerosis, the triad of Charcot is often emphasized as a common, and a diagnostically significant, finding. I notice from Dr. Rupp's report that the triad was not found very frequently as compared with certain other signs and symptoms he mentioned. It certainly does not occur early. Does he have any data on the time of appearance of the triad in the development of symptoms?

DR. MATTHEW T. MOORE: While it is true that the sclerotic plaques in multiple sclerosis involve, in the main, the conducting pathways of white matter, this is not entirely true. My colleagues and I have seen many cases in which the gray matter of the cord has been involved and in which, indeed, the plaques have produced a complete transverse lesion of the cord. In the cerebrum, again, the usual distribution of the plaques is in the white matter in relation to the ventricles. However, we have 2 cases in which the plaques invaded the cortex.

I noted that Dr. Rupp did not include in his report any evidence of muscular atrophy in his cases of multiple sclerosis. This atrophy is not uncommon, and when it is present the disease has been referred to as the amytrophic type of multiple sclerosis.

DR. GEORGE D. GAMMON: The Russian investigators last year claimed to have isolated a virus in 2 cases of acute disseminated encephalomyelitis and to have obtained evidence of antibodies for these two viruses in cases of multiple sclerosis. The inference from this work is that multiple sclerosis is a virus disease.

Was there any indication from the present study which might lend weight to the idea that the spread of an agent, such as the Russian investigators claim might occur in multiple sclerosis, had taken place along discrete pathways?

Have the authors ever seen a positive Wassermann reaction of the spinal fluid in a case of multiple sclerosis? I have had occasion to suspect such an occurrence in a case of true multiple sclerosis without syphilis.

DR. ROBERT A. GROFF: I should like to ask Dr. Rupp about the patients who had pain in the face. Were they considered to have trigeminal neuralgia, and were they treated for this condition?

DR. JOSEPH C. YASKIN: Multiple sclerosis is often misdiagnosed in two ways. First, multiple sclerosis in the early stages is often diagnosed as hysteria. I challenge any neurologist in the United States to state that he has not diagnosed as hysteria (hysterical blindness or paraplegia) a condition which later proved to be multiple sclerosis. Second, other organic conditions, notably tumors of the brain and spinal cord, are often mistaken for multiple sclerosis early in their course. In general, it is best not to be hasty in making too early a diagnosis of multiple sclerosis. Indeed, a diagnosis of early multiple sclerosis is not helpful in treatment, whereas to overlook some other condition amenable to some form of therapy is much more serious.

DR. CHARLES RUPP: With reference to Dr. Schwarz's question, Charcot's triad was always a late sign in these cases. In no case was it a presenting one. It was low on the list with respect to frequency, being present in only 12 cases. I agree with Dr. Moore that multiple sclerosis has no predilection for the long

projection pathways and that it may involve both the gray and the white matter. If our observations on transient lesions of peripheral nerves are correct—and we have no reason to doubt them—the disease may involve also the peripheral nerves. I think the reason that some degree of motor weakness is always present at one time or another in the course of the disease arises from the fact that the voluntary motor pathway is long, and that somewhere, at some time, it is involved to an extent sufficient to give rise to symptoms. Atrophy was present in some cases. Possibly Dr. Riggs could give a tentative statement as to how many. We did not give the exact number, for in a review of case records that went back over twenty-five years it was difficult to ascertain how often the atrophy was the atrophy of disuse and how often it was atrophy due to disease of the anterior horn cells. As I mentioned in the paper, transverse lesions of the spinal cord occurred in 22 cases; certainly, that is good evidence that the gray, as well as the white, matter is involved.

In answer to Dr. Gammon's question concerning the etiologic agent: We did not make a detailed study of the pathologic changes, and I do not think the extent of our survey would justify our making any statement as to the cause.

With reference to whether there is ever a positive Wassermann reaction in cases of multiple sclerosis, no such instance occurred in our series. I suppose a syphilitic person can also have multiple sclerosis, but I do not think it is common.

As to the presence of pain in the face, in the 2 cases in which there were sensory changes in the face, the disturbance was in the form of dysesthesias or paresthesias, rather than distinct pain.

I agree with Dr. Yaskin that multiple sclerosis is often misdiagnosed. It should be borne in mind that in the present case the disease was not in an early stage, and so there was not the likelihood of the misdiagnosis of hysteria being made. People do not usually die of hysteria, and before they do die one has a chance to have a clearer formulation of the exact diagnosis.

Dr. Helena Riggs: I have never seen isolated involvement of the gray matter of the cortex. There is regular and early involvement around the ventricular system, particularly around the posterior horns, the aqueduct and the fourth ventricle.

As to Dr. Gammon's question about the spread of the pathologic process in these cases, this progression could be observed only in cases of the very early acute stage. At autopsy the lesions are those of scar, and nothing can be learned of the nature of the progression. It is interesting to speculate on whether acute multiple sclerosis and chronic multiple sclerosis are one entity. They are probably clinically somewhat alike, but pathologically they are entirely different. In acute multiple sclerosis there is tissue necrosis with proliferation of microglia, both as rod and as gitter cells, whereas in chronic multiple sclerosis the plaques consist mainly of gliosis with the "horsehair" type of glia. I have never seen a lesion in a case of the chronic type in which Deiters' cells were present, and they occur in lesions in the cases of so-called acute multiple sclerosis.

Myelomalacia Secondary to Dissecting Aneurysm of the Aorta. Dr. Gabriel A. Schwarz, Dr. Norman S. Anderson (by invitation) and Dr. Winston K. Shorey (by invitation).

A case of a dissecting aneurysm of the aorta was reported. The aorta was dissected along its posterior aspect from the aortic arch to the renal arteries. The dissection involved the origins of the intercostal arteries on both sides. Many of

the intercostal arteries were torn off and their lumens thrombosed. A flaccid paraplegia developed with loss of all modalities sensation below the level of the eighth or ninth thoracic dermatome bilaterally. Autopsy revealed softening of the spinal cord essentially from the level of the sixth thoracic dermatome down into the lumbar and sacral portions.

The conclusion seemed justified that in certain circumstances the spinal cord may be adequately supplied by an anastomotic arterial system, which may act physiologically as a true end artery system.

DISCUSSION

DR. MATTHEW T. MOORE: I have seen a case of similar involvement of the cord with partial necrosis and myelomalacia secondary to carcinoma en plaque in the epidural space. This caused compression of the vessels supplying the spinal cord, resulting in softening and secondary invasion by the metastatic lesion. In another case there was extensive seeding of the entire spinal cord from a medulloblastoma of the cerebellum, secondary to operation, and several areas of the cord showed transverse myelomalacic lesions. The latter, in all probability, were due to the heavy cuffing of the metastatic lesions, which embarrassed the blood supply to the cord.

DR. ROBERT A. GROFF: I have performed many posterior rhizotomies for the relief of pain. The last one involved section of the nerve roots in the thoracolumbar region. The patients have suffered no ill effects from this procedure. Furthermore, Dr. George Heuer, of New York, has done, and recommended for a time, anterior root section involving practically all the thoracic nerve roots in cases of this condition. The patients suffered no ill effects other than the loss of power associated with the root section.

In the light of this evidence, I wish Dr. Schwarz would explain why we have not seen malacia of the spinal cord in his slides. When the nerve roots are clipped, the vessels contained in these roots are occluded.

DR. JOSEPH C. YASKIN: I am not clear about the anatomic explanation. Myelomalacia associated with Pott's disease, metastatic malignant growths and allied conditions is not due to the interference with the arterial blood supply. It results from the interference with the venous return and is traceable to venous stasis. Thrombosis of the spinal arteries is rare except in syphilis and some other definite infections. Rhizotomies per se do not cause myelomalacia; this is a common observation in any neurosurgical clinic.

DR. HELENA RIGGS: I have been puzzled, as Dr. Schwarz has, about these cases of malacia. I have seen two or three dissecting aneurysms with similar pictures of malacia. In trying to find an explanation, I took all the material with advanced arteriosclerosis of the aorta and found that, though one could not get a fine probe through the arteries, there were not focal lesions in the spinal cord. I formulated a tentative explanation that with a dissecting aneurysm the patient has had a long-standing circulatory insufficiency before dissection occurs and that he has a lower margin of reserve. Not only has the circulation been cut off in the lower thoracic branches, but the blood coming down through the vertebrae will be greatly decreased, since the entire circulation not only through the aneurysm but through the heart and the peripheral circulation, is decreased. Thus, on a slowly progressive circulatory insufficiency is superimposed a disturbance of general circulation and thrombosis of some of the radicular branches. Probably all these factors are necessary before an infarction of the spinal cord is established.

DR. MATTHEW T. MOORE: Dr. Yaskin's statement regarding the role of venous stasis in the pathogenesis of these lesions is correct, but it does not apply to the lesions described by Dr. Schwarz. Where there is acute stoppage of the arterial supply, various stages of liquefaction necrosis follow. The slides shown by Dr. Schwarz indicated that this had occurred, and there was a fading out of the process toward the periphery in the upper reaches of the thoracic portion and in the lower reaches of the lumbar portion of the spinal cord. In the cases that I cited, the histologic and gross studies conclusively indicated that the arterial supply was involved.

DR. GABRIEL A. SCHWARZ: I was interested to hear Dr. Moore mention metastatic myelomalacia. As a matter of fact, in the literature is reported a case of metastatic carcinoma, extraaxial in which there was an area of intense myelomalacia. The softening was within the area of blood supply to the large radicular artery, and was due to the carcinomatous involvement of that artery, not to pressure from the neoplasm.

Dr. L. Tanon showed that if he injected this large artery in the lumbar root he was able to fill the entire arterial system of the spinal cord. He was not able to do so with injections above the ninth thoracic level. Those data have been corroborated by a number of other investigators. In the lumbar and in the lower thoracic region, there seems to be one artery which is most important for the integrity of the arterial blood supply to a goodly portion of the cord.

Dr. Groff had good fortune in clipping the posterior roots in an entire series without any softening of the cord. Most of the posterior root arteries supply only the roots themselves; often they do not enter the spinal cord or supply any blood to the spinal cord. Consequently, if a series of them is clipped off, the circulation to the spinal cord is not interrupted. But if the great radicular artery on the side of the anterior roots were sectioned, I am sure that softening would result.

DR. ROBERT A. GROFF: Heuer suggested cutting the anterior roots for the entire thoracic supply bilaterally, from below the second to the twelfth, in the treatment of hypertensive cardiovascular disease; and he carried out that procedure on many patients. I do not know whether myelomalacia developed in any of them.

DR. GABRIEL A. SCHWARZ: There is a tremendous variation in the blood supply, but I am sure that if he caught this tremendous artery, which is very evident in specimens, he would get myelomalacia over a wide area. The third and fourth lumbar spinal arteries supply only the roots. They do not even reach the spinal cord. The spinal cord in the conus medullaris is supplied entirely through this large artery, and it is usually present on one side.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Leo M. Davidoff, M.D., *President, New York Neurological Society, Presiding*
Joint Meeting, Dec. 9, 1947

Atypical Syndromes Produced by Extramedullary Tumor of the Cervical Portion of the Cord. DR. BERNARD C. MEYER (by invitation) and DR. BERNARD D. FINE (by invitation), Ann Arbor, Mich.

This article was published in full in the March 1949 issue of the ARCHIVES, page 262.

DISCUSSION

DR. IRA COHEN: It is well that we be reminded from time to time, as Dr. Meyer has done this evening, that there are many deviations from the usual or expected pattern of the abnormal. It is important to remember that an operable lesion of the spinal cord may present itself without all the criteria one looks for in an extramedullary tumor. It is also well to remember that an extramedullary tumor of the cord may mimic a combined system disease. For the cogent reasons given by Dr. Meyer, this is seen most frequently in the cervical region.

Since the signs and symptoms of tumors of the spinal cord are in part dependent on mechanical factors, all such factors must be taken into account in explaining the clinical picture. I have in mind the presence or absence of manometric block, the relative percentage of the total protein and, I believe I may safely add, the degree of disability. One must know, therefore, the position of the tumor, its size, its consistency and its vascularity. A small hard tumor strategically placed may cause greater disability without manometric block than a large soft tumor. On the other hand, a large soft tumor may give a manometric block with few clinical signs. The mobility of the tumor and its vascularity may explain some of the variations in the physical signs observed on successive examinations. The part played by the degree of interference with the circulation of the cord itself has not been evaluated except for metastatic lesions.

Although in none of the 7 cases cited in the paper were there anything like all the classic signs of an extramedullary tumor of the spinal cord, each of them presented one or more features that led to the proper management of the case. In 3 cases there was conclusive roentgenographic evidence. In 2 cases pain was increased by elevation of the spinal fluid pressure through coughing or through pressure on the jugular vein. In these 2 cases pain was increased on the patient's assuming the recumbent posture. In the other 2 cases the pain pointed away from a combined system disease that was otherwise suggested. In the cases without changes in the cerebrospinal fluid the clinical picture was suggestive. In the cases in which the clinical picture was against, rather than for, an extramedullary tumor, the laboratory studies supplied the clue.

The obvious conclusion is the age-old one that diagnosis is based on all the facts, clinical and laboratory—that the art lies in the interpretation.

DR. GEORGE H. HYSLOP: I think that those who are interested in medical neurology ought to be reminded that in a case of a cord syndrome in which subjective sensory disturbances indicate a cord level one is not dealing with a degenerative disease. I have too often seen made a diagnosis of degenerative disease, idiopathic or of some other type, because there was no manometric block but the patient had subjective complaints. Of course, one must allow for the dependability of the patient's story.

DR. ISRAEL STRAUSS: I wish to confirm what Dr. Cohen said about the change of symptoms in these cases. I know of few diseases in medicine that do not have variations in symptoms. In listening to the presentation, I heard the words "slight sensory disturbance." There is no such thing as a "slight sensory diturbance"; it is a sensory disturbance or it is not, and sometimes these slight variations can be of great significance. Not long ago I sent into the hospital a patient whose complaint was severe pain in the back when he lay down at night. This symptom was mentioned by the authors as occurring with certain tumors of the cervical portion of the cord. The only clinical sign I could ascertain was

the Babinski reflex, and this was not always present. I sent the patient into the hospital for study, with the tentative diagnosis of a tumor of the spinal cord. Unfortunately for the patient, though in the end it did not matter, he had taken many drugs at night for sleep, and he was therefore discharged from the hospital with the diagnosis of psychoneurosis, after having been thoroughly examined. He died of carcinoma with metastases affecting the spinal cord.

In connection with the case of amyotrophic lateral sclerosis presented, I think that every clinician who has dealt with amyotrophic lateral sclerosis will admit that pain persisting for a long period ought to warn the physician that the condition is not amyotrophic lateral sclerosis. Dr. Cohen's comment on the vascularity of tumors and their extramedullary nature is important, for a patient may go along perfectly well and suddenly become paraplegic; operation reveals a large tumor which had evidently been placed in a favorable position, giving no symptoms, until a disturbance in circulation occurred, perhaps as a consequence of change in the position of the tumor, with subsequent paralysis. I have seen the same thing happen with a lesion of the anterior aspect of the cord, extradural in nature, which pressed on a portion of the cord and caused for a long time a spastic paresis with no sensory disturbance and no interference with the bladder or rectum, but with a certain amount of loss of balance. After an operation carefully done by one of the best surgeons in the city, there was complete paraplegia, with rectal and sphincteric involvement.

Effect of Pathologic Anxiety on Inductive Reasoning. Dr. Livingston Welch (by invitation) and Dr. Oskar Diethelm (by invitation).

This article is published in full, with discussion, in this issue of the Archives, page 87.

Spread of Pain. Dr. E. Charles Kunkle (by invitation), Dr. George C. Armistead (by invitation) and Miss Helen Goodell (by invitation).

The digits of the hand, as distinct projections of the body, are particularly suitable for the study of spread of pain from a site of noxious stimulation. An effective and reproducible stimulus has been found in the immersion of a finger in water maintained at 0 C. Pain thus induced follows a conveniently cyclic course.

In 100 experiments on 22 adult subjects, pain due to cold was nearly always found to overflow to adjacent areas, notably to neighboring digits. Features common to this phenomenon in almost all the experiments were a latent period, facilitation in subsequent phases of the pain cycle, "tapering" of intensity and "incomplete segmental filling." The direction of spread was predominantly caudad in most instances. In no subject was contralateral extension of pain noted. Pain failed to spread from thumb to jaw (in cortical sequence). Overflow of pain was unaltered by preliminary interruption of the circulation to the arm or by procainization of an area into which spread of pain was to occur.

In contrast to these typical features of spreading pain, other, and less "orderly," characteristics were noted. Most prominent was the moderate intraindividual and pronounced interindividual variation in extent of spread. In a minority of instances the spreading pain "migrated" during the experiment, "skipped" a digit or reached a higher intensity than that of the primary pain (insubordination).

Many of these listed features of spreading pain have also been observed in patients with traumatic digital lesions, dental disease or angina pectoris. It is inferred that such overflow of pain is a central phenomenon and probably occurs at the segmental level in the cord. This mechanism contrasts sharply with spread of pain due to a peripheral effect, as in secondary contraction of skeletal muscle, and with reference of pain throughout the domain of a sensory nerve trunk as the result of a proximal nerve or a dorsal root lesion.

Experimental Studies on the Nature of Hyperalgesia. DR. HAROLD G. WOLFF, DR. JAMES D. HARDY (by invitation) and MISS HELEN GOODELL (by invitation).

There are a number of varieties of hyperalgesia. Considered here is the type which can be experimentally induced in areas of skin adjacent to sites of noxious stimulation, as described by Sir Thomas Lewis. In these areas pain threshold is not lowered, although pinprick and thermal stimuli above pain threshold elicit more intense and longer-lasting painful sensations than in control areas. Hyperalgesia develops from tissue injury in a procainized area of the skin as soon as the effect of procaine begins to diminish. After the hyperalgesia has become established, complete procainization of the site of injury immediately eliminates it. Also, the rate of development and spread, as well as the elimination of the hyperalgesia by injection of procaine, are unaffected by occlusion of the blood supply. Hyperalgesia develops in areas adjacent to prolonged thermal radiation inducing no more than threshold to minimal pain, and the hyperalgesia does not persist longer than the stimulation. Pinprick in the zone of hyperalgesia causes the minimal pain from the site of noxious stimulation to be intensified. These observations make it difficult to explain this type of hyperalgesia on the basis of the local liberation of a humoral substance in the sites of the hyperalgesia and makes a special nocifensor system, as postulated by Lewis, unnecessary. On the basis of the foregoing evidence, it is suggested that the hyperalgesia that develops in areas adjacent to a site of noxious stimulation of the skin is dependent on the spread of a central excitatory state which results from a sustained barrage of noxious impulses from the periphery.

DISCUSSION

DR. RAFAEL LORENTE DE NÓ: In attempting to discuss this paper I find myself in a difficult position. I am tremendously impressed by the beauty of the observations and the thoroughness of the method used; there is nothing I can object to, and there is very little I can add to what has been said. One of the most important things in the presentation was the emphasis placed on the need of accurate methods of measurement in experimental work. The great difference in the theoretic results obtained by Dr. Wolff and by Lewis is due precisely to the fact that Dr. Wolff has developed an exceedingly accurate method of measurement, so that he at any moment is capable of stating in physical units the strength of the stimulus employed and to measure the pain. The fact that hyperalgesia developed without any change in the peripheral threshold of stimulation seems to me of tremendous importance in the physiology of pain. It places hyperalgesia in the central nervous system. The problem becomes that of the summation of impulses that have arrived at the nervous system through different pathways. I am entirely in agreement with Dr. Wolff on the need of considering a diagram

of that type, a system of internuncial neurons that takes care of the summation of the stimuli. If one desires, however, to go into detail as to how those systems are built in the nervous system, one finds that the present day knowledge of the anatomy and physiology of the spinal cord is exceedingly limited. In the first place, the anatomy of the spinal cord is so little known that one can postulate many systems and diagrams by using the scant information that exists in the literature, but one cannot with any degree of assurance say that those fibers or neurons one postulates are more than a valuable working hypothesis. I think the physiologists will find the greatest difficulty in explaining the process of the spread that takes such a long time to develop and that disappears instantaneously in the moment that the peripheral stimulus has been removed. The only possible explanation I see is that the continuous arrival of impulses progressively decreases the threshold of certain neurons; a change of this kind will not be effective in producing hyperalgesia unless impulses from the periphery are arriving at the internuncial pool.

Book Reviews

Die multiple Sklerose des Menschen. By Georg Schaltenbrand. Pp. 267. Georg Thieme, Karl Tauchnitzstr. 3, Leipzig C. 1, 1943.

Schaltenbrand's book on multiple sclerosis consists of a review of the literature and a critical appraisal of past work and of various hypotheses concerning the disease, as well as original reports on the author's own experimental and therapeutic work. The book is divided into five major chapters.

Chapter 1 is concerned with manifestations of multiple sclerosis. This chapter includes a review of the geographic distribution and incidence of multiple sclerosis, the typical manifestations of the disease, methods for early diagnosis by objective measurement of the tonic state of the muscles, autopsy findings and the relation of multiple sclerosis to other demyelinating diseases.

Chapter 2, entitled "Theories Concerning the Causation of Multiple Sclerosis," deals with the hereditary aspects of the disease, Putnam's thrombosis theory, the enzyme theory, the infection theory and the allergic theory. In the author's opinion, the weight of evidence is regarded as supporting the theory of infection. Chapter 3 is a complete documentation of the author's animal experiments.

Chapter 4 contains a critical appraisal of chapter 3, as well as protocols of the author's experiments in man, including his transmission experiments from monkey to man and from man to man. It is regrettable that in his work reported in this chapter the author succumbed to the standards of experimentation on human beings which prevailed in Nazi Germany at that time. In this chapter, Schaltenbrand reports, among similar experiments, what he considered the successful transmission of monkey encephalitis from monkeys to a number of psychiatric patients, listing not only the diagnoses of his victims (they were suffering from various illnesses, including brain tumor, arteriosclerosis and schizophrenia) but also their full first names and the first two or three letters of their family names. A total of 35 names are thus listed. Nothing is said in the book as to whether these patients or their next of kin volunteered for these experiments. The results are unconvincing. Repeated reinoculations were used, and the pathologic changes as described and photographed do not convince this reviewer that anything more than the well known Rivers phenomenon was reproduced.

In chapter 5 the conclusions include a discussion of the spinal fluid findings in multiple sclerosis; the relation of multiple sclerosis to aseptic meningitis; the role and possible significance of the involvement of the cranial nerves; the relation of multiple sclerosis to polyneuritis, rheumatism and diseases of the skin; the anemia found in patients with multiple sclerosis, and a brief section, 8 pages long, on prognosis and methods of treatment, as well as one section each on prevention and medicolegal implications.

Of particular interest are Schaltenbrand's statements concerning the therapeutic use of blood and its derivatives, which had been employed earlier by Dumas and Foix in 1924 and by Stransky in 1937 and 1938. Schaltenbrand reported that of the patients with the acute disease whom he treated in 1938 by means of repeated blood transfusions, 50 per cent remained well and employed for five years, whereas in other years, when blood transfusions were not routinely employed, remissions of significant duration were obtainable in an average of only 17 per cent of the patients treated, the figures for the other six years averaging from 6 to 27 per cent. Schaltenbrand does not give absolute figures for the number of patients treated each year, and it appears from the context that his group of cases was comparatively small.

Emotional Security. By Milton R. Sapirstein, M.D. Price, $3.50. Pp. 291. Crown Publishers, 419 4th Ave., New York 16, 1948.

This book is an excellent delineation of psychoanalytic principles. The author has been singularly successful in integrating within limited space the facts and theories of dynamic psychiatry and the pertinent contributions from other fields that bear on human behavior, including biology, cultural anthropology and sociology. He is always mindful of the integer of behavior, who in this era must adapt to a rapidly changing culture; for this person he offers much understanding.

Sapirstein discusses neurosis as a breakdown in the adaptation of a person to the environment, a definition which might serve illness in general. In the first third of the book he considers the causes of breakdown in adaptation and the defenses against anxiety which may develop when the state of equilibrium is disrupted. The basic defenses against anxiety are clearly described under the headings of flight, fight or looking for help. The person's use of these mechanisms determines whether he is healthy or neurotic. The proper amount of flight, fight or help seeking is healthy; the not knowing which of these defenses to use and when is unhealthy and puts a tremendous strain on the organism.

The middle third of the book is perhaps the most mature discussion of sexuality that has appeared of late. Here are described the many attitudes that impinge on sex, and why it is impossible to delineate such a condition as normal sexuality. Adult sexuality and marriage are thoughtfully discussed; the romantic screen is torn aside, to present a lucid consideration of the security that may be had in a mature relationship. The author shows with great clarity that much of the stress surrounding marital sexuality is again a misuse of the three basic defenses against anxiety—flight, fight and the seeking of help.

The final third of the book is composed of chapters on hostility, war neurosis, psychosomatic disorders, creativity and what the patient may derive from psychoanalysis. The chapter on creativeness and originality is particularly stimulating. Too much endeavor has been devoted to finding a neurotic motive for every unusual human creation, and the author makes the exceedingly important point that psychotherapy need be brought to bear only when creativity is paralyzed. Activity must be analyzed not only according to its motivation but also in terms of its effects. In other words, it is more important, generally speaking, to know how a person is functioning than why.

The author has the gift of trenchant summary, examples of which may be seen at the end of his chapters, as well as the ability to draw clear diagrams and relate clinical material interestingly. He is most skilful in seeing the good in many theories, if not in all of them, and in adroit utilization of that which is good from the works of many men. After all, this might be one definition of a good psychiatrist.

This book is highly recommended as one of the best in the welter of psychiatric literature that has poured from the presses of late. It is required reading for anyone training in psychology or psychiatry or for one who wishes to know about human behavior. In fact, it could serve as a textbook wherever psychodynamics is taught.

Confidências de um investigador científico. By Egas Moniz. Price not given. Pp. 629, with many illustrations. Edičoes Atica, Lisbon, Portugal. 1949.

Not many scientists have been pumped full of lead, still less lived to tell the tale and end up by winning the Nobel Prize. However, one of the thrilling passages in this large volume of reminiscences deals with the attack of a homicidal maniac and the resulting convalescence from six bullet wounds.

Egas Moniz is a far more extraordinary character than the one he reveals in his memoirs. Born to opulence in a town where his forebears had resided for a millennium, he entered on a medical career and taught neurology for several years at Coimbra before taking the chair at the newly founded faculty of medicine in Lisbon. During and after World War I he switched to statecraft, returning to his university position in 1923, when he was approaching the age of 50. Up to this point it might be said that his life was one of local and national distinction in one of the smallest and most backward countries of Europe. It is interesting to speculate on what it was that turned this comfortably situated, middle-aged professor, hampered since adolescence with gout, into one of the foremost investigators of his time. Unfortunately, the modesty of the author draws a veil over the inner processes of challenge and response that effected this change; and his gentleness permits only an oblique glimpse of the heart-breaking obstacles placed in his way. Some day it may be hoped that an account of these obstacles, the rivalries, the scorn of his contemporaries and the attempts at thievery of his discoveries may see the light.

The story begins placidly enough, with sketches of his graduate studies in France at the Indian Summer period of Babinski, the Dejerines and Pierre Marie. Cerebral localization was the keynote of their researches. When the war was over, Moniz went again to Paris and learned of the new advances in localization by roentgenography with contrast mediums. "One day I thought of arterial injection. I did not know whether arteries had been punctured. This ignorance did not jeopardize the work. It was obvious that lipiodol could not be used. Some other fluid had to be employed that would be innocuous when injected into the cerebral arteries. . . . And in these lucubrations I went along from 1924 to the last months of 1926."

The period of gestation of these lucubrations was a long one, but the eventual results were extraordinary. Finally, a safe and effective method was found for cerebral angiography. Within two years others not only had adopted the method, but had reported it without mention of Egas Moniz. It was several years before the author was able to establish his claim to discovery. There followed a long period of further development, perfection, description, attendance at international meetings and writing of monographs in several languages. Egas Moniz' position was secure as one of the great contributors to the field of neurology. By 1935, when the Second International Neurological Congress was held in London (where he demonstrated his films in the scientific exhibit), cerebral angiography was being learned by a host of followers.

It was probably two years before this, in 1933, when arteriographic studies were still in full swing, that a second stroke of genius came to Moniz. Again, the period of gestation was a long one. Two years elapsed before his idea was ripe for discussion. Then, at the same meeting in London, a symposium on functions of the frontal lobe acted as a catalyst, and he began in earnest his studies on prefrontal leukotomy. "The destruction of cellular connections of the cerebrum in psychotic patients in such a way as to alter the nerve currents into new pathways was the first conception, which, although fundamentally organic was not very acceptable to those who buried themselves in the meanderings of dialectics of psychopathology more or less to the limits of the metaphysical.

"So I confided to Almeida Lima the secret of my aspiration and the speculations that were running through my mind, cautioning him to secrecy."

Discoveries come to the prepared mind. The symposium in London was devoted to the defects that resulted from injuries of various sorts to the frontal lobes. Surely, nobody else came away from that session with the idea that destruction could be beneficial to the patient with an intact brain. Egas Moniz,

however, had been pondering the subject of cerebral cellular activity in connection with mental disorder. The number of cells is fixed, and their cell bodies show no change. It is the connections that are changeable. Extremely variable in the normal person, these connections can be altered into more or less fixed patterns of activity by the constant association of certain stimuli. This had been shown by the researches of Pavlov. The underlying anatomic and physiologic substrate is the synapse, as indicated by Ramón y Cajal. "The cellular-connective groupings, rapidly formed and rapidly transformed in new and successive combinations, are, in my opinion, the anatomophysiologic basis of the psychic life. . . . Delusional and melancholic ideas, hypochondriasis, anxiousness and ideas of persecution dominate the mental activity of the sick person. These perturbations must be related to the formation of cellular-connecting groups that are abnormally stabilized. . . . Disturbance in these arrangements would liberate patients from their morbid mental activity, permitting them to bring into action other cellular-connecting groups. This is the principle that directed my operative endeavors."

In November 1935, Almeida Lima, under Moniz' direction, injected small quantities of alcohol into the white matter of the frontal lobe through two trephine openings. A month later, the injections gave way to surgical division of the fibers. In June 1936 Moniz' classic monograph "Tentatives opératoires dans le traitement de certaine psychoses" was published by Masson, in Paris. He also published several other papers in various countries at approximately the same time. Moniz was taking no chances on further piracy.

In contrast with the immediate and warm reception granted the work on angiography, there was little or no response to papers on leukotomy. In fact, the method was almost abandoned in Lisbon after a few more months. The author passes lightly over the obstructions that were placed in his path. Then came the homicidal attack with its prolonged convalescence, followed by the outbreak of World War II, and in 1944 Egas Moniz retired, at the age of 70. He was unable to report any large series of cases or any considerable body of catamneses. Instead, he returned to his first field of investigation and published three more monographs on various phases of cerebral angiography.

Recognition came late to Egas Moniz, but then with increasing volume, culminating in the First International Conference on Psychosurgery, held in Lisbon in August 1948. The author draws both on his recollections and on his scrapbooks for an unusually full account of the activities connected with this meeting. He closes almost on a pastoral note, written from his ancestral home. As this review goes to press news comes that he has been awarded the Nobel Prize.

This large volume of reminiscences is concerned largely with happenings. Space is given to the author's ideas concerning medical education, scientific discoveries and scientific method; to interpretations of the work of various authors in terms of Moniz' own experiments, and to various speeches and papers concerning himself and his work, written by others. The author thus reveals a certain modésty that appears almost exaggerated. The book will particularly appeal to readers who have praised Egas Moniz, since they will find their words quoted *in extenso*. The approach is objective; little or no space is given to speculations regarding the author's mental mechanisms. Even the attempt at assassination is described almost with detachment:

"'It was a poor lunatic. Call my wife. I should like to see her before I die.'

"'They put me on the chaise longue in my consulting room.'

"'Go call an ambulance,' someone said.

"'Let me die here in peace. I've been mortally wounded. He couldn't miss me with his shots. I couldn't resist.'"

Actualités de neuro-chirurgie. By G. Guiot. Price, 450 francs. Pp. 86. Gaston Doin & Cie, 8 Place del'Odéon, Paris 6^{e}, 1948.

This small book is essentially a collection of the author's previous studies assembled under one cover. There is, first, a good summary of the symptomatology of tumors of the temporal lobe. Meningiomas of the sphenoidal ridge are divided into internal, intermediate and external varieties, the type depending on the point of origin along the ridge. The symptomatology of these three varieties is outlined. Craniopharyngioma is next discussed, and then the symptomatology of occipital tumors, and a brief note on adenomas of the hypophysis is appended. All these discussions are clear, concise and traditional and contain nothing new.

The corneopterygoid reflex is described in detail. First observed in 1902 by Solder, it has not attracted much attention. Guiot states the belief that it is produced by a direct or indirect lesion of the brain stem; a more accurate localization is not possible.

Guiot used iodized oil in the ventricles in cases of hydrocephalus to determine whether or not the interventricular foramens are open. The medium must be injected in very small quantity—not more than 0.33 cc. The globule is rolled about and observed fluoroscopically.

Chapter 2 is concerned with closed head injuries. The various stages of development of the symptoms are detailed. The state of consciousness is depended on largely to determine the condition of the patient. One determines whether the patient responds to questions (superior consciousness), whether he reacts to excitations (automatic consciousness) and whether he swallows (instinctive consciousness). In spite of the misuse of the word consciousness (conscience), the directions given are of great practical usefulness. Otherwise, the discussion follows traditional lines.

Chapter 3 is a discussion of cerebral edema, a subject which greatly interested the Pitié clinic. Vincent distinguished passive edema, the result of stasis, and active edema, the result of arterial or arteriolar dilatation with serous transudation. This is a phenomenon which greatly interests the surgeon but disappears at death, so that it is not apparent to the pathologist. The different conditions in which it has been observed are described. The author believes that scars may produce physiologic arrest of function, not only in peripheral nerves but also in the spinal cord and brain.

The second part of the monograph contains a detailed and useful account of the various stages in the development of compression of the spinal cord. The author insists that when the compression is removed the recovery of the function follows the same stages in reverse; and they may be passed quickly. These stages are paraparesis, spastic paraplegia, hyperspastic paraplegia, flaccid-spastic paraplegia and flaccid paraplegia.

The third part is devoted to therapeusis. Guiot describes a useful approach to the brain stem which may be used to reduce herniation of the temporal lobe through the incisura tentorii, to cut the spinothalamic tracts in the mesencephalon or to open the basal cisterns. This section is original and should prove useful to neurosurgeons. Brief sections on the treatment, of epilepsy of unknown cause, of tuberculoma of the cerebellum and of cerebral abscess, together with a note about intravenous administration of procaine, complete the book.

One gains from the perusal of this book a good impression of the neurosurgery being done in France. It is recommended to the attention of all neurologists.

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